CHARACTERISTICS OF MULTIPARAMETRIC MAGNETIC RESONANCE IMAGING IN PROSTATE CANCER DIAGNOSTICS AND ACTIVE SURVEILLANCE

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DOCTORAL DISSERTATION

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To Maija, Erik and Elias

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Abbreviations

5-ARI	5-alpha-reductase inhibitor
ADC	apparent diffusion coefficient
ADT	androgen deprivation therapy
AR	androgen receptor
AS	active surveillance
BCR	biochemical recurrence
BPH	benign prostate hyperplasia
bpMRI	biparametric MRI
Bx	prostate biopsy
CAB	complete androgen blockade
CAPRA	Cancer of the Prostate Risk Assessment score
CI	confidence interval
CSS	cancer-specific survival
cTNM	Clinical Tumor, Node, Metastasis classification system
DCE	dynamic contrast enhancement
DRE	digital rectal examination
DWI	diffusion-weighted imaging
EAU	European Association of Urology
EBRT	external beam radiotherapy
EPE	extraprostatic extension
ERG	v-ets avian erythoblastosis virus E26 oncogene homolog gene
FBx	magnetic resonance imaging/ultrasound-fusion targeted prostate biopsies
fPSA	free circulating prostate-specific antigen
FSH	follicle-stimulating hormone
GG	International Society of Urological Pathology (ISUP) Grade Grouping
GS	Gleason score
GU	Gleason score upgrading
HDR-BT	high-dose rate brachytherapy

HIFU	high-intensity focused ultrasound
HK2	human Kallikrein 2
IADT	intermittent androgen deprivation therapy
IGRT	image-guided radiotherapy
IMRT	intensity-modulated radiotherapy
IQR	interquartile range
LH	luteinizing hormone
LHRH	luteinizing hormone-releasing hormone
LN	lymph nodes
LNM	lymph node metastases
MRI	magnetic resonance imaging
mpMRI	multiparametric MRI
NPV	negative predictive value
NRS	numeric rating scale
MSKCC	Memorial Sloan Kettering Cancer Center
OC	organ confined
OR	odds ratio
OS	overall survival
PCA3	prostate cancer antigen 3
PHI	prostate health index
PI-RADS	Prostate Imaging Reporting and Data System
PTEN	phosphatase and tensin homolog
pTNM	Pathological Tumor, Node, Metastasis classification system
PRIAS	Prostate Cancer Research International: Active Surveillance
proPSA	inactive proenzyme form of prostate-specific antigen
PSA	prostate-specific antigen
PSA-DT	prostate-specific antigen doubling time
PCa	prostate cancer
RALP	robot-assisted laparoscopic prostatectomy
RCT	randomized controlled trial

ROC	receiver operating characteristics
ROI	region of interest
RP	radical prostatectomy
SBx	systematically targeted prostate biopsies
SPCG	Scandinavian Prostate Cancer Group
SVI	seminal vesicle infiltration
TC	treatment change
TMA	tissue micro array
TMPRSS2	transmembrane protease serine 2
TNM	Tumor, Node, Metastasis classification
TRUS	transrectal ultrasound
T2WI	T2-weighted imaging
US	ultrasound
WW	watchful waiting

List of original publications

This thesis is based on the original publications listed as follows:

I. **Repeat multiparametric MRI in prostate cancer patients on active surveillance.** Eineluoto JT, Järvinen P, Kenttämies A, Kilpeläinen TP, Vasarainen H, Sandeman K, Erickson A, Mirtti T, Rannikko A. PLOS ONE. 2017; 12; DOI: 10.1371/journal.pone.0189272

II. **Patient experience of systematic versus fusion prostate biopsies.** Eineluoto JT, Järvinen P, Kilpeläinen TP, Lahdensuo K, Kalalahti I, Sandeman K, Mirtti T, Rannikko A. European Urology Oncology. 2018; 1; 202-207. DOI: 10.1016/j.euo.2018.02.005

III. **Associations of PTEN and ERG with magnetic resonance imaging visibility and assessment of non-organ confined pathology and biochemical recurrence after radical prostatectomy.** Eineluoto JT, Sandeman K, Pohjonen J, Konrad S, Nordling S, Sturenberg C, Malén A, Kilpeläinen TP, Santti H,. Petas A, Matikainen M, Pellinen T, Järvinen P, Kenttämies A, Rannikko A, Mirtti T. European Urology Focus. 2020; DOI: 10.1016/j.euf.2020.06.016

IV. **Prostate MRI added to CAPRA, MSKCC and Partin cancer nomograms significantly enhances the prediction of adverse findings and biochemical recurrence after radical prostatectomy.** Sandeman K, Eineluoto JT, Pohjonen J, Erickson A, Kilpeläinen TP, Järvinen P, Santti H, Petas A, Matikainen M, Marjasuo M, Kenttämies A, Mirtti T, Rannikko A. PLOS ONE. 2020; 15; DOI: 10.1371/journal.pone.0235779

Author's contributions

Study I

Concept and design

Acquisition of data

Analysis and interpretation of data

Drafting the manuscript

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Study II

Concept and design

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Statistical analysis

Study IV

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Drafting the manuscript

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Statistical analysis

Abstract

Prostate cancer (PCa) is the most common non-cutaneous male malignancy in the world. The diagnosis is challenging. Too many clinically insignificant, but not all clinically significant PCas are found. Active surveillance (AS) is an approach to monitor clinically insignificant PCas and, when needed, offer curative treatment to patients in a timely manner. Multiparametric magnetic resonance imaging (mpMRI) with its structured imaging reporting system (PI-RADS), and biomarker analysis of histopathology may aid diagnosing the clinically significant PCas.

In Study I, we focused on depicting the performance of repeated mpMRIs in an AS cohort. During AS, patients underwent multiple prostate biopsies (Bx) to obtain histopathological specimens for detecting the possible development of PCa. Bx sampling may cause Bx-related side effects, such as discomfort and even re-hospitalization for patients. In Study II, we compared patient experience in two groups receiving either systematically targeted prostate biopsies (SBx) or mpMRI/ultrasound fusion targeted Bxs (FBx). We assessed the accuracy of mpMRI further in Study III by comparing mpMRI visible (true positive) and mpMRI invisible (false-negative) tumor lesions when we matched their locations with the histopathological analysis of radical prostatectomy (RP) specimens. We also assessed the risks for biochemical recurrence (BCR) and analyzed PTEN and ERG biomarker expressions and their roles in mpMRI visibility. In Study IV, we addressed the benefits of mpMRI as an addition to Partin tables, Memorial Sloan Kettering Cancer Center (MSKCC) nomogram and Cancer of the Prostate Risk Assessment Score (CAPRA) risk score, i.e. traditional risk stratification tools in PCa.

Main results: I: PCa progression was seen in 69% of patients using mpMRI. High-risk PI-RADS scores of 4-5 associated with treatment change (TC) from AS to active treatment. Tumor progression on repeated mpMRIs associated with TC. **II:** Patients in the FBx vs SBx groups received a median of three vs 12 Bx cores. The FBx group reported significantly less pain and hematuria at 30 days after Bx. Patients who were willing to undergo rebiopsy reported lower pain and discomfort scores and less fever than unwilling patients. **III:** Patients with mpMRI invisible lesions had higher BCR-free survival time and fewer adverse findings (extraprostatic extension, seminal vesicle invasion and lymph node metastasis) than mpMRI visible lesions. Loss of PTEN biomarker staining was more common in mpMRI visible lesions. **IV:** Models with mpMRI outperformed the models with only clinical data, MSKCC nomogram and Partin tables for the prediction of adverse findings in RP. Survival analysis for BCR revealed that mpMRI separated the curves significantly in CAPRA and MSKCC risk nomograms.

Conclusions: mpMRI depicts changes in PCa during AS and seems beneficial in patient diagnosing and monitoring. During AS, where multiple Bxs are needed over years, FBx causes less harm for the patient than routine SBx. mpMRI invisible lesions appear less aggressive than mpMRI visible lesions as indicated by aggressive cancer growth beyond the prostate. PTEN loss is associated with aggressive types of PCa, and was more often seen in mpMRI visible than mpMRI invisible tumor lesions. Finally, adding mpMRI to traditional risk stratification models with clinical data is beneficial in the detection of aggressive types of PCa.

Tiivistelmä

Eturauhassyöpä on miesten yleisin syöpä. Nykyään tunnistetaan liikaa kliinisesti merkityksetöntä syöpää, joka ei vaikuta elinajanodotteeseen. Toisaalta, kaikkia aggressiivisia, kliinisesti merkityksellisiä syöpiä (csPCa) ei pystytä tunnistamaan riittävän ajoissa. Kliinisesti merkityksettömiä syöpiä todetessa potilaita voidaan aktiiviseurata (AS), jolloin pidättäydytään välittömästä hoidosta. AS aikana voidaan edetä hoitoihin, mikäli csPCa:ään viittaavaa ilmenee. Eturauhasen multiparametrinen magneettikuva (mpMRI) raportoituna stukturoidun lausunnon (PI-RADS) mukaisesti sekä biomarkkerianalyysit kudosnäytteistä saattavat auttaa csPCa:n tunnistamisessa.

Osatyössä I tutkimme mpMRI:n ominaisuuksia AS:n aikana. Potilailta otettiin useita kertoja koepaloja eturauhasesta, jotta mahdolliset aggressiiviset syöpäpesäkkeet tunnistettaisiin. Koepalojen otto voi aiheuttaa kipua, infektioita ja jopa sairaalahoitoja. Osatyössä II vertailimme potilaiden raportoimaa tyytyväisyyttä ja haittavaikutusten määrää systemaattisen koepalaoton (SBx) tai mpMRI-ultraäänikohdennetun koepalaoton (FBx) jälkeen. Osatyössä III verrattiin mpMRI:ssä näkyviä ja näkymättömiä syöpiä eturauhasen poistoleikkauksen kudosnäytteisiin. PTEN- ja ERG-biomarkkerien ilmaantuvuutta kudosnäytteissä ja leikkauksenjälkeistä laboratoriokokeissa havaittavaa syövän uudelleenaktivaatiota (BCR) vertailtiin mpMRI:n kykyyn tunnistaa syöpäpesäkkeet. Osatyössä IV arvioitiin mpMRI:n hyötyä tavanomaisten syövän riskilaskurien, kuten Partinin taulukoiden, MSKCC-nomogrammin ja CAPRA-riskipisteytyksen, apuna csPCa:n tunnistamisessa.

Tulokset: I: mpMRI:ssä näkyi syövän muttuminen aggresiivisemmaksi 69%:lla potilaista. Korkean syöpäriskin PI-RADS-pisteet 4-5 mpMRI:ssä liittyivät potilaan siirtymiseen AS:sta aktiivihoitoon. Syövän muuttuminen aggressivisemmaksi toistetussa mpMRI:ssä liittyi AS:sta aktiivihoitoon siirtymiseen. **II:** FBx- ja SBx-ryhmissä potilailta otettiin kolme ja 12 koepalaa (mediaani). FBx-ryhmässä raportoitiin vähemmän verivirtsaisuutta ja kipua 30 vrk kohdalla toimenpiteen jälkeen. Potilaiden halukkuus uusintabiopsiaan toimenpiteen jälkeen liittyi vähäisempään raportoituun kipuun ja epämukavuuteen. **III:** mpMRI:ssä näkymättömät syövät liittyivät parempaan ennusteeseen BCR:n ja syövän aggressiivisten muotojen (syövän kasvu eturauhasen kapselin ulkopuolelle, seminaalivesikkeleihin ja imusolmukkeisiin) suhteen verrattuna mpMRI:ssä näkyviin pesäkkeisiin. PTEN-biomarkkerin puutos oli tyypillisempää mpMRI:ssä näkyvissä kuin näkymättömissä syövissä. **IV:** MSKCC-nomogrammi ja Partinin taulukot yhdessä mpMRI:n kanssa olivat parempia tunnistamaan syövän aggressiivisia muotoja kuin pelkkä tilanteen arviointi kliinisesti tai riskilaskurit yksinään. mpMRI oli hyödyllinen BCR:n tunnistamisessa verrattuna pelkkään CAPRA-riskilaskurin tai MSKCC-nomogrammin käyttöön.

Johtopäätökset: mpMRI tunnistaa syövän muutoksia AS aikana ja näyttää olevan hyödyllinen eturauhassyövän diagnosoinnissa ja seurannassa. AS aikana otetaan useita kertoja koepaloja eturauhasesta ja FBx-koepalat aiheuttavat vähemmän haittavaikutuksia kuin SBx-koepalat. mpMRI:ssä näkymättömät syöpäpesäkkeet ovat vähemmän aggressiivisia kuin näkyvät pesäkkeet. PTEN-biomarkkeripuutos kudosanalyysissä liittyi syövän aggressiivisiin muotoihin ja sitä tavattiin useammin mpMRI:ssä näkyvissä kuin näkymättömissä syövissä. mpMRI:n käyttö perinteisten riskilaskurien lisäksi on hyödyllistä csPCa:n tunnistamisessa.

1. Introduction

Prostate cancer (PCa) is the most common non-cutaneous malignancy in men in the western world. It is a disease characterized by a high prevalence and a low mortality, and PCa represents up to 28% of new cancer diagnoses and 13% of cancerous causes of death in Finland [1]. Typically, the PCa patient is a Caucasian aged 50 to 70 years and lives in western countries [2].

The diagnosis of PCa is typically based on the prostate-specific antigen (PSA) test, digital rectal examination (DRE) and prostate histopathological samples (biopsies, Bx). Usually 12 systematically targeted Bx cores (SBx) are taken and they cover the entire prostate. However, due to the random nature of these Bxs, i.e. the Bxs are not visually targeted for a tumor lesion, diagnostic accuracy is a compromise. SBx may miss the most aggressive form of PCa present in the prostate (i.e. underdiagnosis). Bxs may also detect clinically insignificant PCa (i.e. overdiagnosis), and cause complications such as pain, discomfort and infections [3]. Furthermore, PSA is not a cancer-specific laboratory test and DRE may miss anterior cancers that extend beyond the prostate capsule. Therefore, new diagnostic tools are needed to detect better the clinically significant, i.e. large, aggressive and potentially lethal, PCa (csPCa), while also avoiding a diagnosis of clinically insignificant "indolent" cancers. The variable nature and heterogeneous phenotype of the disease is likewise problematic regarding diagnosis. PCa is often multifocal and may develop over time. The least aggressive forms of PCa are localized, small and unifocal cancers, and don't affect patient's life expectancy (i.e. clinically insignificant PCa). The clinically insignificant PCas can therefore be monitored by active surveillance (AS). AS is an established and accepted form of treatment and is typically based on repeated DRE, PSA, and Bxs during follow-up. The main goal of AS is to defer radical treatment when not immediately needed. If suspicion of more aggressive forms of PCa arise, patients are referred to active treatment.

Multiparametric magnetic resonance imaging (mpMRI) may aid in diagnosing csPCa more accurately. Contemporary mpMRI combines anatomical imaging with functional assessment and a structured reporting system such as Prostate Imaging Reporting and Data system (PI-RADS) [4]. When compared with SBxs, mpMRI has been shown to detect more csPCa, and less clinically insignificant PCa [5-8]. mpMRI can also be used for targeting PCa lesions in the prostate. A combination of MRI and ultrasound (US), known as fusion Bx (FBx), combines an accurate MR image with a live US image. This allows clinicians to potentially target PCa lesions that are visible on mpMRI, but not visible in US. By targeting PCa lesions in this way fewer samples are taken, thus causing fewer complications that arise from sampling. However, FBx is limited when a PCa lesion is invisible under mpMRI, and the lesion cannot be targeted. Hence, FBx may not fully replace SBx until the clinical characteristics of mpMRI invisible lesions are known.

Biomarkers, such as Phosphatase and Tensin Homolog (PTEN) and v-ets avian erythroblastosis virus E26 oncogene homolog gene (ERG), are another approach to improve diagnostics. Loss of a tumor suppressor gene PTEN is shown to be associated with adverse findings in RP specimen [9-11]. By detecting these biomarkers in Bxs, the potentially aggressive forms of PCas can probably be detected and radical treatment can be given in a

timely manner. Thus far, PTEN and ERG have not yet gained wider clinical acceptance. Instead, risk stratification of PCa patients is accomplished using conventional tools, such as risk calculators and nomograms.

The aim of this PhD project was to contribute to the efforts of improving PCa diagnostics by diagnosing only csPCa but not the insignificant PCa. Studies I and II focus on an AS population and investigate the role of repeated mpMRI and the experience and complication rates of patients undergoing FBx. Studies III and IV focus on RP patients, they elucidate the role of the biomarkers PTEN and ERG. They also investigate mpMRI invisible PCa lesions, and present conventional risk stratification nomograms combined with mpMRI.

2. Literature review

2.1 The prostate

The word prostate originates from mid-17th century and comes from the Greek words “pro” and “statos”, translated as “one that stands before” [12]. The prostate is a key member of the male reproductive system. It is a gland that surrounds the urethra and it is located in the pelvis between the bladder, rectum and pubic symphysis. Formation and development of the prostate occurs between gestational weeks 8-36. Prostate growth is induced by androgens and the post-pubertal weight of the prostate is approximately 20 grams [13].

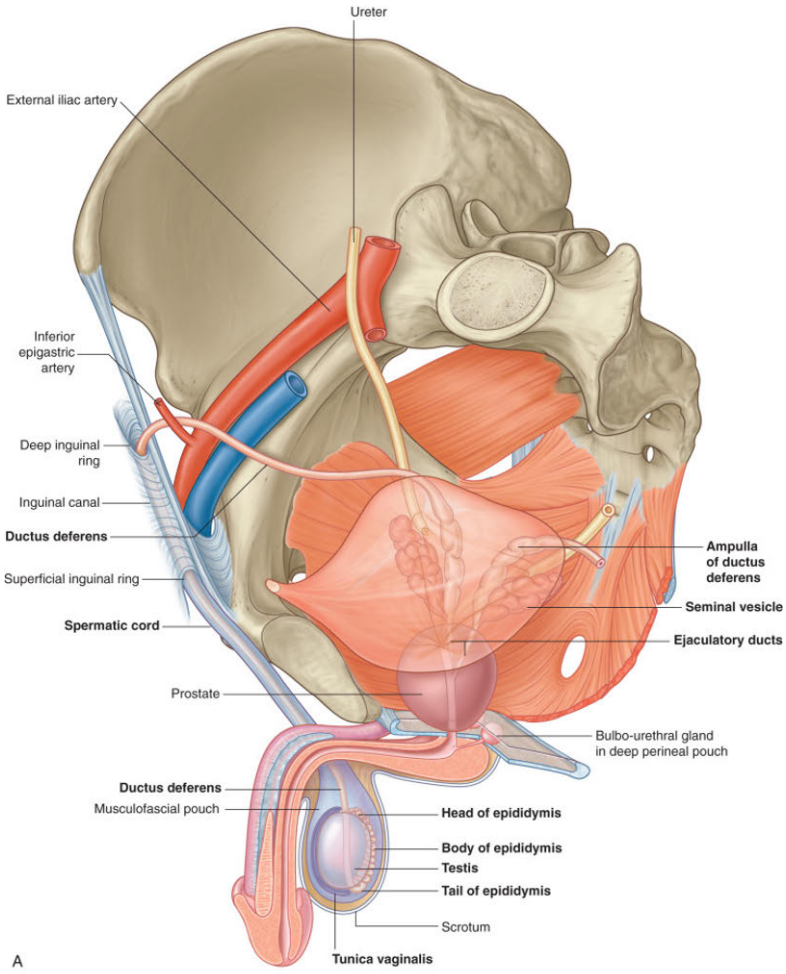

Figure 1. The genitourinary tract of a man. Reprinted from Gray’s Anatomy for Students 4th edition, Copyright 2020, with permission from Elsevier, accessed Mar. 10, 2020.

Sperm are produced in the testicles, then they are stored and matured in the epididymis and subsequently secreted into the urethra by the ejaculatory ducts. The ejaculatory ducts of the prostate open into the urethra. Prostatic fluid and the fluid secreted by the seminal vesicles are added to sperm. This mixture is called the ejaculate (semen). The prostatic secretion is accountable for 30% of the volume of semen. PSA is a glycoprotein secreted by the epithelial cells of the prostate gland. It is a constituent of semen. Its only known function is the liquefication of semen to allow sperm move towards to the ovum. This enzymatic action of PSA and other kallikrein proteins is crucial to male fertility [14].

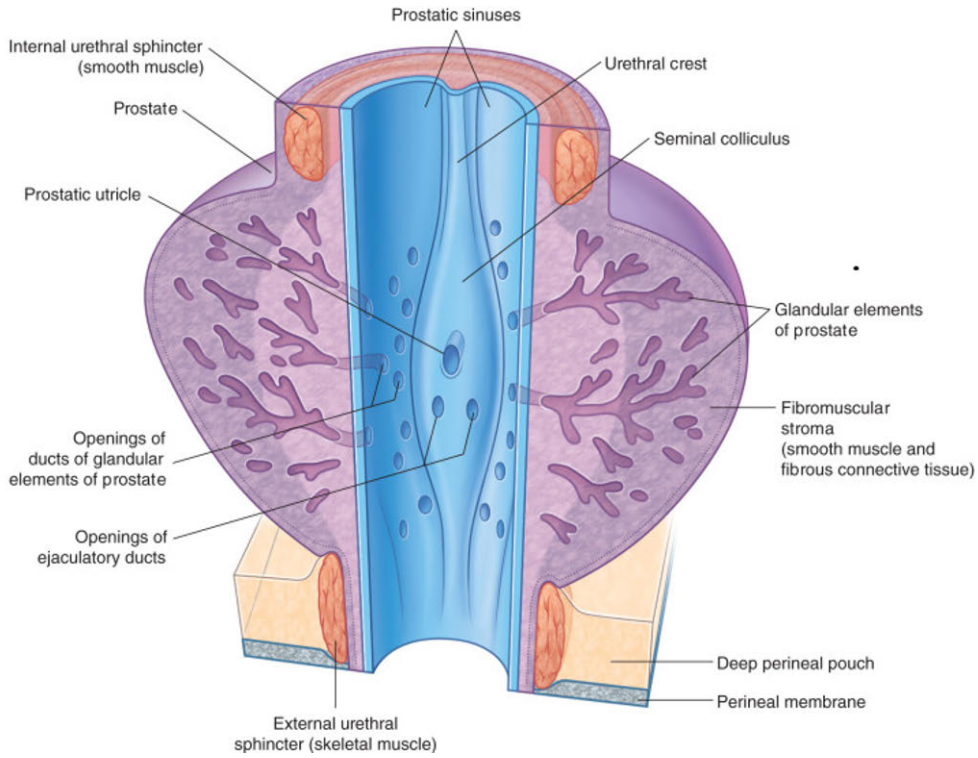

Figure 2. Prostatic urethra and ejaculatory ducts. Reprinted from Gray's Anatomy for Students 4th edition, Copyright 2020, with permission from Elsevier, accessed Mar. 10, 2020.

The prostate can be divided into three or four zones as depicted in Figure 3 [15]. The peripheral zone contributes 70% of the whole gland volume. Between 70 to 80% of all PCa originate in this area. The central zone includes the openings of the ejaculatory ducts and constitutes of 25% of glandular prostate volume. Only approximately 2.5% of PCas originate in the central zone [16]. The transition zone surrounds the prostatic urethra and is the location of obstructive urinary disorders caused by PCa or benign prostate hyperplasia (BPH). About 20-30% of PCa arise in the transition zone. The fourth, anterior zone, consists of more fibromuscular and less glandular structures [15].

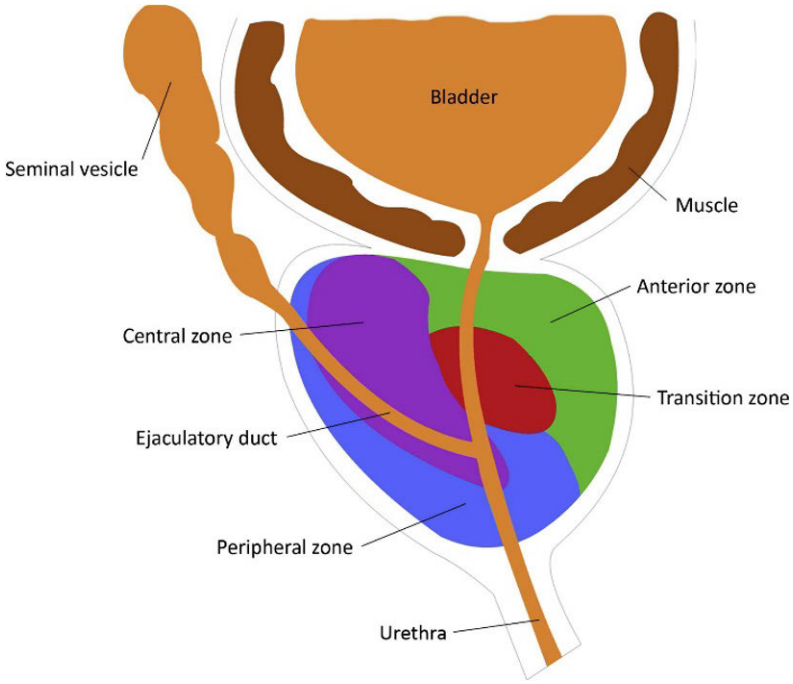

Figure 3. Zones of the prostate. Modified from Franz et al. Zinc transporters in prostate cancer. Mol Aspects Med, Copyright 2013, with permission from Elsevier, accessed Mar. 26, 2020.

2.2 Prostate cancer

2.2.1 Definition

PCa is the most common male malignancy and it accounts for 15% of all cancers diagnosed worldwide [2]. Up to 95% of PCa are adenocarcinomas. The remaining 5% comprise for example lymphomas and sarcomas. This academic dissertation focuses solely on prostate adenocarcinoma. PCa is usually encountered in the peripheral zone of the prostate. When diagnosed, the vast majority of PCas are multifocal, i.e. they consist of multiple cancer lesions inside the prostate gland. The most typical sites of metastases are the lymph nodes (LN), bones, and lungs.

2.2.2 Risk factors

The well-known risk factors for PCa are age, family history of PCa and individuals with African ethnicity. The risk of harboring a high-risk (Gleason score [GS] ≥8 and/or T3-4 and/or PSA ≥20ng/ml and/or N1 and/or M1) PCa on a population level is 1.4%. However, the risk increases several fold, up to 11.4% in men at the age of 65 whose father and two brothers had PCa [17]. The lifetime risk of having any PCa is dependent on age, and at the

age of 65 the risk is 4.5% of any form of PCa [17]. Genetic predisposing factors for PCa have also been investigated, and BRCA2 gene mutation carriers seem to have increased risk of early-onset aggressive PCa [18].

PSA testing has become a widely adopted part of "the men's health check-up" and this increases the lifetime risk of being diagnosed with any PCa (clinically significant or insignificant PCa). This phenomenon is sometimes referred to as "opportunistic screening", i.e. non-systematic and non-organized cancer screening with no proven net benefit for the man. According to a recent long-term follow-up of a PCa prevention trial cohort (PCPT-trial), only every sixth man of the study population harbored any PCa [19].

Metabolic syndrome (diabetes, obesity, high blood cholesterol levels, high blood pressure) has been shown weakly and non-significantly to associate with PCa. According to a recent meta-analysis, among the single components of metabolic syndrome only waist circumference of >102cm and hypertension were significantly associated with PCa [20]. However, the results vary geographically. Another meta-analysis revealed that elevated total cholesterol, high-density lipoprotein, and low-density lipoprotein levels were not associated with a higher risk of PCa [21].

The association of medication and the risk of PCa has been and still is being widely studied and many medications, including metformin, statins, NSAID and thiazide diuretics, are known to alter PSA levels [22]. A population-based study with more than 134 000 patients suggested that metformin use is associated with a reduced risk of PCa (Odds Ratio [OR] 0.84; 95% confidence interval [CI] 0.74-0.96) when compared with non-users [23]. The same effect was not however evident with other oral antihyperglycemic medicine. Metformin is assumed to inhibit cancer development and progression directly. Statins are used to lower blood cholesterol levels, and are associated with lower PSA levels among users when compared with non-users [24]. Statins were also shown to inhibit pathways important to cancer cells [25]. It is unclear whether low PSA levels achieved by statins prevent PCa or delay the diagnosis of advanced PCa [24,26,27]. All in all, a recent large meta-analysis with over 6700 men concluded that statins could not be associated with any or high-risk PCa among men with a negative baseline Bx [28].

5-alpha-reductase inhibitors (5-ARIs) have been suggested to play a role in preventing PCa. Finasteride and dutasteride are used mainly for urinary symptoms caused by BPH. It seems that the use of 5-ARIs reduces PSA levels by up to 50% and also reduces the risk of clinically insignificant PCa (GS 6) while also increasing the detection rate of csPCa [29,30]. A study of over 18 000 men showed that 5-ARIs lower PSA, which might delay the diagnosis of PCa, and thereby increase the risk of advanced (GS 7 to 10) PCa [31]. However, after 18 years of follow-up, there were no differences between the finasteride group and placebo group in rates of overall survival (OS) or survival after diagnosis of PCa [31]. Thus, it is likely that the increased detection rate of csPCa in men who take 5-ARIs relates to improved diagnostics (smaller prostate, i.e. biopsies are more likely to hit the csPCa lesion). So far, 5-ARIs have no indication for PCa prevention. 5-ARIs cause other well-known side effects, such as sexual dysfunction, and, therefore, their use and potential benefit and harm must be discussed with the patient [32]. Testosterone therapy has also been suggested to cause PCa, because the treatment of PCa is crucially linked to androgen deprivation therapy (ADT). So far, long-term evidence on this is absent, but a study with a median follow-up of five years among

1000 hypogonadal men receiving long-term testosterone therapy showed no signs of increased risk of PCa [33].

A western diet seems to increase the risk of PCa [34]. Obesity is shown to be associated with a lower risk for low-grade PCa (OR 0.79; 95% CI 0.65-0.94; p=0.01) but a higher risk for high-grade PCa (OR 1.28; 95% CI 1.01-1.63; p=0.042) [35]. A western type diet therefore seems to increase the risk for PCa and a number of studies on different substances have been conducted to find out if dietary interventions can affect the natural course of PCa. Red meat or processed red meat did not have an association with PCa in a large meta-analysis [36]. Long-chain omega-3 polyunsaturated fatty acids were also not associated with PCa [37], whereas fried food was shown to increase the risk of PCa by 35% in a recent meta-analysis [38]. A cohort of over 35 000 relatively healthy men was studied to ascertain whether the consumption of selenium and Vitamin E could prevent PCa. Selenium and Vitamin E alone or any combination of these substances did not have a preventive effect on PCa [39]. Phytoestrogen intake, however, has been shown to lower the risk for PCa in a large epidemiological study [40]. So far, the European Association of Urology (EAU) guidelines suggests no certain diet for the prevention of PCa [41].

2.2.3 Incidence and prevalence

Men with newly diagnosed PCa are typically between 50 and 70 years and the natural development of the disease occurs slowly. Autopsy studies show that the risk of harboring PCa grows with ageing: each subsequent decade increases the likelihood of harboring PCa (OR 1.7; 95% CI 1.6-1.8) [42,43]. Men from different geographical regions and countries carry a different risk of being diagnosed with PCa. The risk of having PCa is the greatest in well-developed regions such as North America (97.2, age-standardized rate per 100 000 men), Western and Northern Europe (94.9 and 85.0, respectively) and in Australia/New Zealand (111.6). In contrast, Eastern Asia (10.5) and South-Central Asia (4.5) show very low incidences of PCa [44].

In Finland, 5016 new PCa diagnoses and 914 deaths due to PCa were reported in 2018, which represents 28% of all new cancer diagnoses and 13% of all deaths due to cancer in men [1]. The incidence was 76.6 per 100 000 men in 2018 [1,2]. At the same time, PCa prevalence in Finland was over 55 000 representing 44% of all prevalent cancers in Finland [1,45].

2.2.4 Histology of prostate cancer

Up to 95% of PCa consist of adenocarcinomas. The remaining 5% of PCa comprise e.g. lymphomas and sarcomas. Primary urothelial carcinoma without bladder extension accounts for 1-4% of PCas [46]. Sarcomas of the prostate, leiomyosarcoma being the most common variant, are rare and account for only around 0.1% of all prostate malignancies [47]. Lymphomas are also a rare but very lethal form of PCa and they may occur as a secondary infiltration to the prostate among patients whose primary lymphoma is in remission [48]. Neuroendocrine PCas are rare, and they are associated with a poor prognosis [49,50]. After castration or ADT, neuroendocrine cells in prostatic tissue may activate and gain a survival benefit over other cell types, thus initial adenocarcinoma may transform to

neuroendocrine type cancer [51]. This is especially true for men with metastatic PCa that is treated with novel hormonal treatments (CYP17-inhibitors and anti-androgens), for which eventually up to 50% of metastatic lesions may show neuroendocrine differentiation in Bxs [52]. Very rare types of PCa are mucinous carcinomas [53], in which extracellular mucin accounts for up to 25% of tumor volume, and small cell carcinoma [54], which may be present as a solitary foci in an otherwise typical adenocarcinoma. Many small cell carcinomas express neuroendocrine markers, such as chromogranin A and neuron specific enolase, and also have a very poor prognosis [54]. High-Grade Prostatic Intraepithelial Neoplasia (High-grade PIN) seems to precede PCa in most of the cases, and if encountered in a Bx, this should lead to a suspicion of PCa [55].

2.2.5 Mortality and prognosis

In Finland, 914 men died of PCa in 2018, which represents 13% of all male cancer deaths. PCa is the second most common cause of cancer death in Finland is preceded by only lung cancer [1]. Worldwide, PCa caused 358 989 deaths in 2018 and this represents 6.7% of all cancer deaths preceded by lung, liver, stomach and colorectal cancers. African populations and their descendants carry a higher risk of having a clinically significant and even lethal PCa variant with high mortality rates (Caribbean 29 deaths per 100 000 men; Sub-Saharan Africa between 14 to 19; compared with South and Central Asia of only 2.9) [56].

PCa is a heterogeneous disease and so is its prognosis. Low-risk PCa may not affect life expectancy at all. However, according to a large study with over 900 patients, median OS with newly diagnosed M1 disease is around 42 months [44].

2.3 Diagnosis of prostate cancer

2.3.1 Digital rectal examination and transrectal ultrasound

DRE is a method that involves the palpation of the prostate enabling the identification of abnormal extensions that may be PCa. The majority of PCas are located in the peripheral zone of the prostate and, therefore, they can be detected by DRE. Up to 18% of PCa cases have been reported to be detected by DRE alone [57]. The EAU guidelines for PCa advice to perform DRE in addition with PSA for both asymptomatic and symptomatic men to determine whether Bxs are needed [41].

Transrectal ultrasound (TRUS) is an imaging tool that is widely used in urological outpatient clinics. It is primarily used to visualize the prostate, seminal vesicles and periprostatic areas, measure the gland's dimensions and look for tissue homogeneity or abnormal protrusions around the prostate. TRUS can also be used to target Bxs. However, TRUS alone is an insufficient tool to detect focal PCa reliably [58]. TRUS-guided Bxs are the current standard in obtaining histological specimens of the prostate for PCa diagnosis. The transperineal approach to prostate Bxs is also available and in no way inferior to transrectal approach in

terms of PCa detection and complication rate [59]. TRUS-guided Bxs are taken under local periprostatic anesthesia, which usually provides sufficient pain control for the procedure.

2.3.2 PSA

PSA is also known as human kallikrein 3 and it is part of the human kallikrein protein family. PSA secretion mainly occurs from the prostate but some minor amounts of PSA can be found in breast tissue, in adrenal and in renal carcinoma [60]. PSA was discovered in the 1970s and later the PSA test was introduced to clinical practice in the USA in the 1980s. The use of PSA spread rapidly and by the 1990s the PSA test was already in wide use by the Nordic countries [61]. PSA is used as a tumor marker. Tumor markers can be developed for blood tests that are used by physicians to help detect malignancies. Ideally, tumor marker values increase only when a malignancy is present and not for other non-malignant reasons. However, it was soon noticed that PSA is an organ-specific but not a cancer-specific marker, and its levels also rise for reasons other than the presence of PCa, which include prostatitis, prostatic manipulation, and BPH. Moreover, it was soon realized that the concentration of PSA also increases with age due to increasing prostate size, and the rate of rise of PSA is approximately 3.2% per year [62]. In addition to this patients with a very low PSA levels can also harbor a csPCa. This makes the use of PSA in PCa screening problematic.

The rate at which PSA rises is, however, useful when considering whether a patient might require further diagnostic procedures [63]. PSA velocity is the increase in PSA over time usually one year (ng/ml/year). However, a short prostate-specific antigen doubling time (PSA-DT) has not been linked to adverse findings [64]. Today, the EAU guidelines advise that PSA-DT and PSA velocity do not offer useful information in PCa diagnostics when compared to PSA alone [41].

The introduction of PSA to clinical use and its effect on PCa incidence and mortality in Finland can be seen in Figure 4 [1]. There was a surge in number of diagnosed PCa after the discovery of PSA in the 1990s, but the found PCas had very little, if any, effect in PCa mortality. Hence, the majority of newly diagnosed PCas were low-risk cancers that did not affect life expectancy.

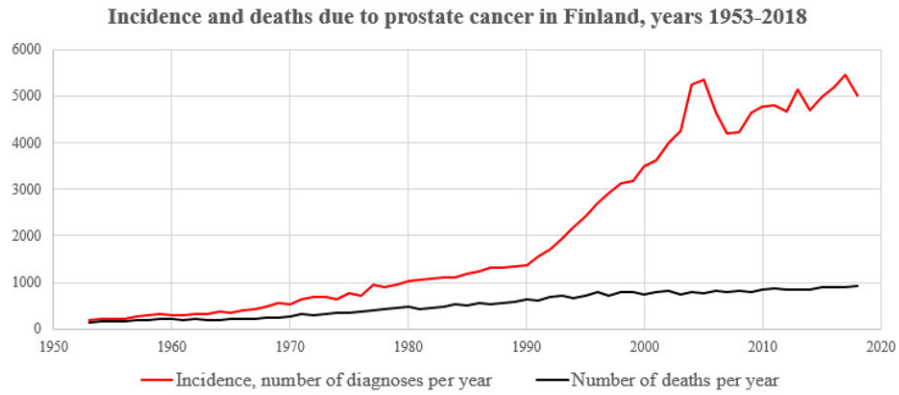

Figure 4. Incidence and mortality due to prostate cancer between 1953 and 2018 in Finland. Modified from Cancer Registry Finland (https://cancerregistry.fi)

2.3.3 Prostate biopsy

2.3.3.1 Systematic biopsy

Upon deciding who would benefit from Bxs, traditionally PSA, DRE, and additional risk stratification tools have been used to decide whether Bx is needed [41]. Prior to the procedure, the patient should be informed of the advantages, such as early diagnosis and adequate treatment in a timely manner, and also of the disadvantages, such as diagnosis of clinically insignificant PCa and anxiety that it generates. In addition the risks to the patient associated with the Bx procedure are another consideration. The standard procedure is TRUS-guided Bx. Antibiotic prophylaxis is given prior to procedure to prevent infections. Antibiotic guidelines vary due to differences in bacterial resistance rates locally. Quinolones were usually the drug of choice for their proper tissue concentrations [3], until the European Comission banned fluoroquinolones in March 2019 due to their adverse side effects and rising concerns of bacterial resistance [65]. At the time of writing, the EAU guidelines have not yet adapted this regulation. SBxs are taken in a sextant pattern, equally from left and right lobes, medially and laterally, usually resulting in 12 biopsy cores, which seems to be a compromise between diagnostic accuracy and Bx-related side effects [66]. Typical complications include lower urinary tract symptoms, hematuria, hematospermia, rectal bleeding and infections. Septic infection is the most feared complication and it is encountered in 1-3% of cases at significantly varying rates [3,41]. Data suggest that SBx with 12 cores suboptimally predicts RP findings in up to 40% of patients [67]. Moreover, AS cohort studies with RP or confirmatory Bx show GS upgrading in 20 to 30% of the cases [68,69]. Hence, either PCa is multifocal and SBx does not always find the most adverse cancer focus or PCa may also develop over time.

2.3.3.2 Targeted biopsy

Targeting PCa lesions in the prostate can be performed either cognitively (trying to aim at lesions detected by US or MRI) or using fusion techniques (in-bore, MRI/TRUS). MRI-targeting of Bx with fusion techniques (FBx) has been available now for some years. Patients go through a prostate MRI prior to Bx procedure and using technical applications the MRI image is fused with a TRUS image as the patient typically lies in lateral recumbency or in the supine position. This fusion allows the region of interest (ROI) seen on the MRI, but not in TRUS, to be targeted using FBx more accurately (Figure 5). Fusion techniques include not only MRI/TRUS-fusion, but also direct in-bore Bxs, where patient is in the MRI suite and targeted Bxs are taken using real-time MRI guidance [70]. No superiority between cognitive, in-bore or mpMRI/TRUS-fusion techniques has been reported, so far [41,71]. The inter-operator reproducibility of mpMRI-targeted Bxs has not yet been evaluated, so even if mpMRI detects csPCa the Bx procedure itself may not be useful for all operators.

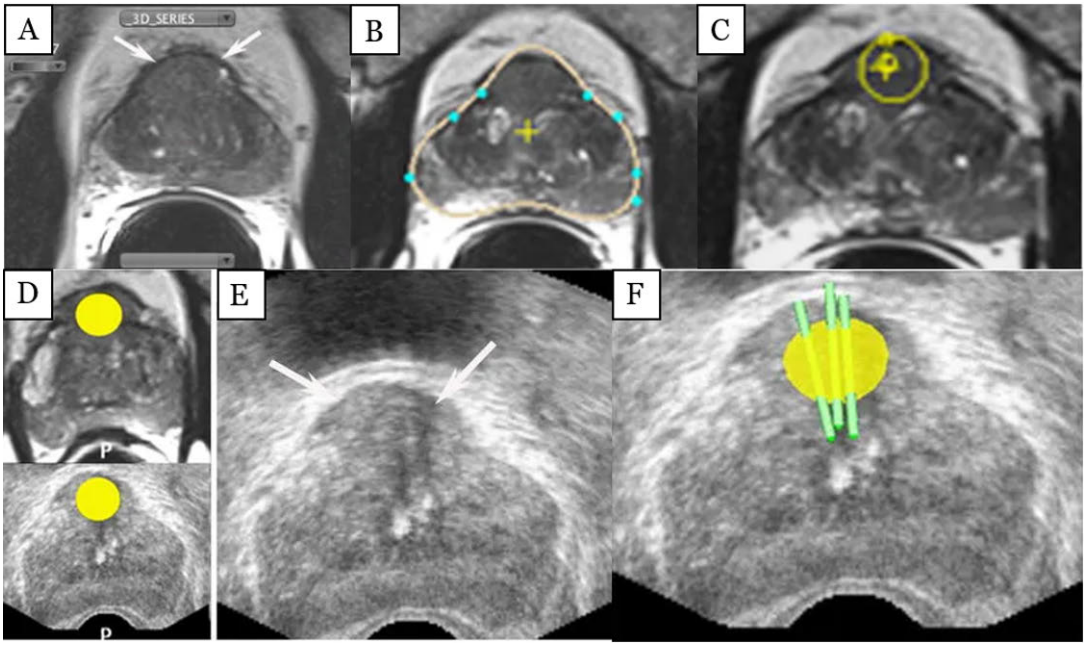

Figure 5. MRI-ultrasound fusion prostate biopsy. A) Identification of a prostate cancer lesion in multiparametric MRI; B) Drawing an outline of the prostate; C) Highlighting and marking the tumor; D) MRI-ultrasound fusion image visualizes the lesion in transrectal ultrasound; E) The tumor is otherwise not clearly visible in transrectal ultrasound; F) Targeted biopsies can be taken from the tumor. Reprinted by permission from Copyright Clearance Center: Springer. Abdominal Imaging. TRUS-MRI image registration: a paradigm shift in the diagnosis of significant prostate cancer, Cornud et al., Copyright 2013.

2.3.4 Classification of prostate cancer

2.3.4.1 TNM

Patients with similar histological PCa types and clinical outcome are pooled using the WHO Tumor, Node, Metastasis (TNM) classification system [72]. The TNM system is divided into two different branches the first being clinical TNM (cTNM), which comprises DRE, TRUS, mpMRI, computer tomography (CT) and bone scan. The second branch is pathological TMN (pTNM), which refers to histopathological tissue analysis of the prostate and seminal vesicles after RP (Table 1).

T - Primary Tumour (stage based on digital rectal examination [DRE] only)	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T1	Clinically inapparent tumour that is not palpable
T1a	Tumour incidental histological finding in 5% or less of tissue resected
T1b	Tumour incidental histological finding in more than 5% of tissue resected
T1c	Tumour identified by needle biopsy (e.g. because of elevated prostate-specific antigen [PSA])
T2	Tumour that is palpable and confined within the prostate
T2a	Tumour involves one half of one lobe or less
T2b	Tumour involves more than half of one lobe, but not both lobes
T2c	Tumour involves both lobes
T3	Tumour extends through the prostatic capsule
T3a	Extracapsular extension (unilateral or bilateral)
T3b	Tumour invades seminal vesicle(s)
T4	Tumour is fixed or invades adjacent structures other than seminal vesicles: external sphincter, rectum, levator muscles, and/or pelvic wall
N - Regional (pelvic) Lymph Nodes[1]	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
M - Distant Metastasis[2]	
M0	No distant metastasis
M1	Distant metastasis
M1a	Non-regional lymph node(s)
M1b	Bone(s)
M1c	Other site(s)

Table 1. Clinical Tumor Node Metastasis (TNM) classification of prostate cancer. [1] Metastasis size up to 0.2cm can be designated as lymph node metastasis. [2] If >1 metastasis sites are present, the most advanced category site is used. Modified from Brierley et al. TNM Classification of Malignant tumors, 8th Edition, Copyright 2017, John Wiley and Sons. Reused with permission under a Creative Commons Attributions License, accessed Mar. 6, 2020.

2.3.4.2 Gleason score and ISUP Grade Grouping

The most commonly used method to grade PCa is GS. It was first published by a pathologist Dr. Gleason in 1966 [73]. The difference between commonly used WHO grading and Gleason grading is that instead of the cell nucleus, emphasis in GS is given to the glandular structure. The patterns of prostate glands were pooled by their histopathological appearance and a numerical value was given. The glandular architecture ranges from 1 to 5, i.e. from uniform and concordant to unorganized and infiltrative. The GS is the sum of the most common and the second most common pattern values in histological analysis with a sum value that ranges from 2 to 10. When only one pattern is present, this value is doubled. When three different patterns are present in Bxs, the GS consists of the most common and the most aggressive pattern, irrespective of its extent.

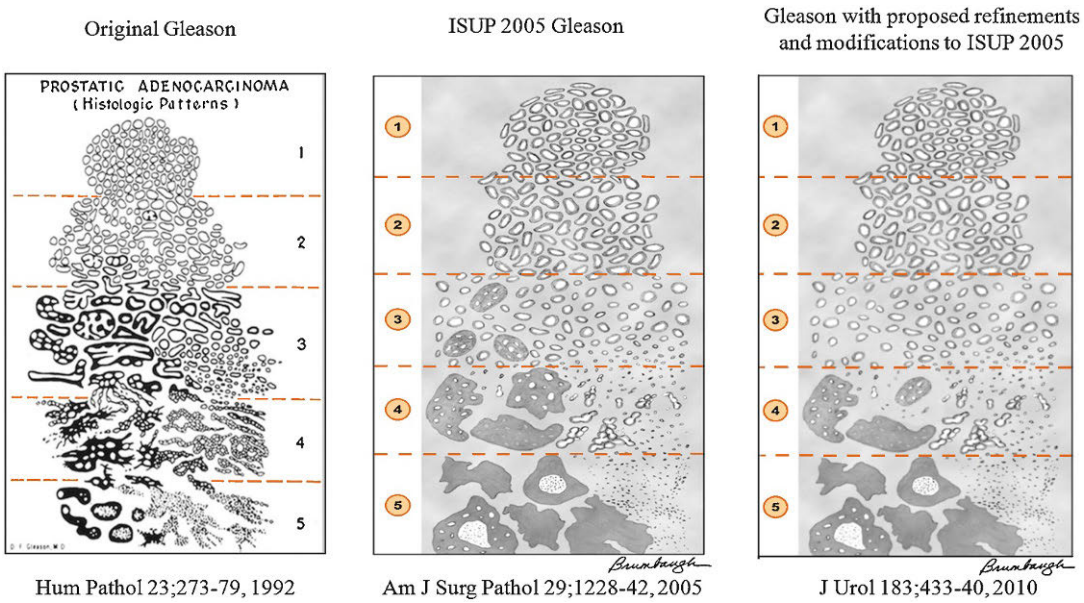

Figure 6. Gleason scoring system illustrating the differences in cell patterns between Gleason scores 1 to 5 and the changes in the scoring system after the two consensus meetings. Modified from Brimo et al. Contemporary Grading for Prostate Cancer: Implications for Patient Care. Eur Urol, Copyright 2013, with permission from Elsevier, accessed Mar. 20, 2020.

Two major consensus meetings have since modified the GS grading system. The ISUP 2005 consensus meeting suggested many changes to the system inter alia Gleason grade 1 was no longer diagnosed as cancer, and the criteria of Gleason grade 3 to 5 were altered (Figure 6) [74]. Later in 2014, another consensus meeting further modified these rules [75]. A new system for grading histological specimen of the prostate was also introduced. The system is based on a large study of over 20 000 men with PCa, and their probability for biochemical recurrence (BCR) during ten years of follow-up after radical treatment [76]. The study

results distinguish five groups that are linked to the patients' GS [76] (see Table 2). This grading system is called the International Society of Urological Pathology Grade Grouping (GG), and it makes a better distinction between the significant, more aggressive and the non-significant forms of PCa (Table 3). The GG comprises values that range from 1 to 5, which makes it easier to understand for patients. A GS 6 out of 10 may sound like an intermediate type of PCa, but GG 1 out of 5, gives a better view on the aggressiveness of that specific type of PCa.

Gleason Score	ISUP Grade Grouping
2-6	1
7 (3+4)	2
7 (4+3)	3
8 (4+4, 3+5 or 5+3)	4
9-10	5

Table 2. The equivalent of ISUP Grade Grouping to Gleason score. Modified from Mottet et al. 2016. www.uroweb.org

Low-risk prostate cancer	Intermediate risk	High-risk	
PSA <10ng/ml GG 1 cT1-2a	PSA10-20ng/ml GG 2-3 cT2b	PSA >20ng/ml GG 4-5 cT2c	any PSA any GG cT3-4 or cN+
Localized			**Locally advanced**
GG = ISUP Grade Grouping; PSA = Prostate-specific antigen			

Table 3. Risk stratification of prostate cancer.
Modified from Mottet et al. 2016. www.uroweb.org

2.3.5 Prostate MRI

MRI has been used in medical imaging since the 1980s. Initially MRI was used in PCa imaging to assess the location and regional staging of patients with a prior positive Bx. With time, technical advancements resulted in a better understanding of the capabilities of MRI. Today, MRI is used in the differentiation of malignant and benign tissues in the prostate and surrounding areas. MRI supports the following objectives: tumor detection, risk stratification, assessment of suspected recurrence and image guidance for Bxs, focal and radiation therepies, and even surgery.

Prostate MRI uses 1.5T or 3T magnetic field. T2-weighted imaging (T2WI) depicts the zonal anatomy of the prostate [77]. Normal peripheral zone tissue is water-rich and has a bright or high-intensity appearance in T2WI. Cancer tissue has higher cellularity and lower water content, and therefore PCa located in the peripheral zone are poorly defined and have low-signal intensity thus creating a contrast with the normal tissue [77]. Conditions such as prostatitis, atrophy, and Bx-related hemorrhages may depict similar round images in T2WI to those of PCa and therefore low-signal intensity focus does not always indicate PCa

exclusively [77]. The transition zone has less water and therefore PCa tumors appear darker in T2WI. PCa in the transition zone manifests with indistinct margins and has low-signal intensity. BPH in transition zone may also mimic PCa appearance. Nonetheless, T2WI is the best at predicting the peripheral zone of the prostate [77]. Another imaging modality used is diffusion-weighted imaging (DWI), which is a functional technique that measures Brownian motion of water molecules in the tissue [77]. Changes in the strength and duration of the magnetic field (indicated by a b value) leads to differences in water diffusion between tissues, which can be depicted in images. DWI b values can be used to create an apparent diffusion coefficient (ADC) map, where cancer appears as low-intensity dark spots [77]. As a further investigation of tumor angiogenesis, T1WI are acquired prior, during and after the administration of an intravenous contrast medium, typically gadolinium. This is called dynamic contrast enhancement (DCE) imaging. These images are interpreted in terms of focal enhancements suspicious of cancer. Additional values including time-to-peak-concentration, and wash-in or wash-out times, can be calculated to recognize patterns typical of PCa [77].

Magnetic spectroscopy imaging can be used for analyzing cellular metabolite concentrations in prostatic tissue. Healthy prostatic tissue has high levels of citrate, whereas cancer tissue has decreased values of citrate and elevated values of choline. Elevated choline-to-citrate ratios form the basis of distinguishing PCa tissue from healthy tissue [77].

2.3.5.1 Biparametric MRI

Biparametric MRI (bpMRI) is one way to perform prostate imaging. It is defined as T2WI and DWI sequences without the use of DCE. Compared to mpMRI, bpMRI is faster, cheaper to perform and carries fewer risks as no contrast medium is administered. The images are also faster to interpret: an mpMRI requires 45 minutes for imaging and 21 minutes for image interpretation on average, whereas the corresponding times for bpMRI are only 15 minutes and 16 minutes [78]. bpMRI seems to be equally accurate as mpMRI in diagnosing PCa in treatment-naïve patients, albeit the heterogeneity of the studies warrants caution in the interpretation of data [79-81]. A study compared the detection rates of csPCa between mpMRI and bpMRI, using either Bx or prostatectomy specimen as a reference, against the performance of the radiologists who had 1, 3 and 7 years of expertise [80]. They found no statistically significant differences either in the performance of the radiologists interpreting the images of the 85 patients or between the imaging modalities [80]. The BIDOC study was a prospective, single-center study that evaluated csPCa (GS≥4+3, or GS≥3+4 and >50% cancerous core length) detection rates for 1020 Bx-naïve patients [81]. That study compared the Bx-naïve patients' bpMRI results with the standard Bx route (SBx) and also a combined Bx route (SBx plus FBx). Patients were assigned to the combined Bx route when their bpMRI showed a suspicion of csPCa. There were no statistically significant differences in csPCa detection rates between the standard Bx and combined Bx groups. FBx was performed for 715/1020 men (70%), and the remaining 305 men (30%) received only SBx. Of these 305 men with negative MRI, who received only SBx, 8/305 men (3%) were diagnosed with csPCa. The negative predictive value (NPV) of bpMRI for ruling out csPCa was 97%. Thus, almost 30% of the study population could have been spared Bx when bpMRI results were

available. However, their reference standard was prostate Bx, not whole-gland prostate specimen after RP [81].

Even though bpMRI has many advantages in comparison to mpMRI, the lack of DCE affects the quality of the images and therefore the use of bpMRI should be restricted to patients with no prior PCa treatments [82]. mpMRI is suggested to be performed instead of bpMRI for men under the following circumstances: high suspicion of csPCa, ongoing or prior surgical or medical intervention of the prostate (including 5-ARIs or testosterone), prior operation of hip implants, after a prior negative bpMRI and persistent suspicion of csPCa, after a prior negative Bx or during AS [82]. Even though the need for DCE in prostate imaging is currently debated, bpMRI seems to be more cost-effective than mpMRI and may thus gain popularity in the future [78]. To date, the EAU guidelines do not recommend the use of bpMRI [41]. Further studies are needed to determine if imaging can be performed on treatment-naïve patients in a biparametric setting without DCE [82].

2.3.5.2 Multiparametric MRI

MpMRI is currently the most up-to-date method to visualize the prostate. It combines anatomical imaging with physiologic and functional assessment including DCE, DWI and ADC [4]. The European Society of Urogenital Radiology has created imaging criteria in order to gain the best images of the prostate [83]. mpMRI is fairly accurate at PCa detection. When preoperative mpMRI images are matched with RP whole-mount specimens, it has been shown that mpMRI will detect large and high-grade tumors. Small (<0.5cm) and less aggressive (GG 1) tumors are not easily detected, which makes mpMRI an ideal tool for detecting more csPCa (GG ≥2) and fewer clinically insignificant PCa [5-7].

To date, there are four high-quality prospective multicenter studies that have assessed the performance of mpMRI in PCa diagnostics. These are the PROMIS [5], the PRECISION [84], the 4M [85], and the MRI-FIRST [86] studies.

First, the paired-cohort PROMIS trial (n=576) was published in 2017 [5]. The authors compared the detection rates of csPCa (GS≥7) in mpMRI and SBx with template Bx as a reference standard. The patients were biopsy-naïve and the Likert scoring system was used for mpMRI interpretation. mpMRI was more sensitive (93%; 95% CI 88-96% vs 48%; 95% CI 42-55%; p<0.001) and less specific (41%; 95% CI 36-46% vs 96%; 95% CI 94-98%; p<0.001) than SBx. The reported NPV for mpMRI for GS≥4+3 PCa was 89%, but lowered to 76% when the cut-off was set to GS≥3+4. No targeted biopsies were performed in this study, and SBx was taken after template prostate biopsies, hence the hemorrhage and swelling of the prostate may have affected SBx results, as no targeting using TRUS was feasible.

Second, the PRECISION trial, published in 2018, compared 500 biopsy-naïve men, who were suspected for csPCa due to elevated PSA levels [84]. Patients were randomized into SBx and FBx groups. All men underwent mpMRI, and if no suspicion of cancer was evident, no Bx was offered. If a PI-RADS 3-5 lesion(s) were seen, men in the FBx group were offered a targeted Bx only, and men in the SBx group were offered a SBx only. For the FBx group 71/252 men (28%) had no suspicion of cancer, hence they did not undergo any Bx. In the

FBx vs SBx groups comparison, csPCa (GS≥3+4) was detected in 95/252 (38%) vs 64/248 (26%) men, respectively (p=0.005). Insignificant PCa was less prevalent in the FBx (9%) vs SBx (22%) group (p<0.001) comparison. The follow-up time was, however, absent from this study. It is likely that in the future, the authors will publish long-term follow-up results of this study cohort. The participating centers also had experienced radiologists who read a median of over 300 prostate MRIs yearly.

Third, the 4M study published in 2019, investigated 626 biopsy-naïve men with a PSA ≥3 ng/ml and a suspicion of PCa [85]. This study compared the detection rates of csPCa (GS ≥3+4 or GG≥2) between the SBx pathway (mpMRI and SBx) and the FBx pathway (mpMRI, SBx, and in-bore FBx). The men were assigned to the FBx pathway if they had PI-RADS 3-5 lesion(s) in their MRIs. The study authors reported no statistically significant differences in the csPCa detection rates between the FBx pathway (159/626 men, 25%) or the SBx pathway (146/626 men, 23%). Detection rates for insignificant PCa was significantly lower in the FBx pathway vs the SBx pathway (14% vs 25%, p<0.001). The follow-up time was one year. The FBx pathway showed negative mpMRI in 309 men, and among these, SBx detected csPCa at a prevalence of only 10/309 (3%). After one year of surveillance the prevalence had risen to 13/309 (4%). No reference RP data were available for this study.

Fourth, the MRI-FIRST trial involving a population of 251 men was published in 2019 [86]. All patients were biopsy-naïve and underwent an mpMRI prior to Bxs. All men underwent SBx, and those with suspicion of csPCa (Likert score 3-5 in mpMRI) also underwent FBx. There were no significant differences in the detection rates of csPCa (GS ≥3+4) in the FBx pathway (mMRI, SBx + FBx) (29%) or the SBx pathway (mpMRI and SBx) (32%; p=0.4). csPCa would have been missed in 5.2% of the study population had SBx not been done, and in 7.6% had FBx not been done. The detection rates for csPCa were highest when the two Bx methods were combined. FBx in the MRI-FIRST detected fewer low-grade, and low volume tumors than SBx. The swelling and hemorrhage after SBx may have affected FBx targeting and the results. As in the case of the PRECISION trial, no follow-up time was presented in this study.

The results of these four prospective, multicenter trials are similar: i.e. FBx detects more csPCa than SBx, and mpMRI has high NPV. This implies that if an mpMRI shows no suspicion of PCa, csPCa is also unlikely in the histopathological samples.

A recent large meta-analysis of over 14 000 patients reported a higher overall detection rate of csPCa (1.16; 95% CI 1.09-1.24; p<0.001) and lower detection rate for clinically insignificant PCa (0.66; 95% CI 0.57-0.76; p<0.001) when using the FBx than when using the SBx pathway [87]. The authors reported no significant differences between biopsy-naïve and previous biopsy-negative cohorts. Another review of 13 845 patients compared the detection rate of any, clinically significant, high-grade, and clinically insignificant PCa [88]. Compared to SBx, FBx was associated with 15% higher risk of any PCa (95% CI 10-20; p<0.001), 11% higher risk of csPCa (95% CI 0-20; p=0.05), and 2% higher risk for high-grade PCa (95% CI 1-4; p=0.005). There was no difference in clinically insignificant PCa between FBx and SBx pathways. Similar results to other meta-analyses were seen in a large Cochrane review of over 6800 men that compared FBx to SBx, with different groups assigned for Bx-naïve and for those with a prior negative Bx [8]. The review reported that overall sensitivity for FBx detecting csPCa was 0.70 and a specificity of 0.96, which

outperformed the TRUS SBx detection rates (0.63 sensitivity and 1.00 specificity). The same Cochrane review recommends performing mpMRI prior to Bx among Bx-naïve men suspicious of harboring csPCa. Furthermore, the EAU guidelines recommend mpMRI to be performed for those patients with a suspicion of PCa who are either Bx-naïve or have prior negative Bx [41].

mpMRI also has its limitations. Using FBx and omitting SBx is beneficial due to the decrease of Bx-related complications but a proportion of PCas are missed. The increased proportion of missed PCas consists largely of low-risk PCas however, and is estimated to be between 4-30% of the study cohort undergoing only FBx [85,88-92]. Whether SBx can be omitted is currently debated [93]. The increasing use of mpMRI also requires resources and the effect on healthcare costs must be further evaluated. Thus, to gain the best results for csPCa detection, SBx and FBx should both be performed, but this elevates the risk for Bx-related complications and also increases the burden on healthcare systems.

mpMRI is also used during AS. A consensus statement by Briganti et al. encourages the use of mpMRI to either rule out the presence of csPCa at the initial diagnosis of low-risk PCa, or before having a confirmatory Bx at 12 months in AS [94]. Targeted Bxs along with SBx are recommended when PI-RADS lesions ≥3 are seen. The role of mpMRI during AS and its ability to replace repeat Bxs is debated. So far, the evidence in favor of serial mpMRI instead of serial Bxs comes only from single-center studies with allegedly established routines and expertise for imaging [94-96]. To date, mpMRI and FBxs solely, cannot be recommended to replace repeat Bxs [41,97] and PSA and mpMRI only are insufficient for AS [98].

2.3.5.3 Prostate Imaging Reporting and Data System (PI-RADS)

The increasing use of mpMRI has led to a need of a structured image reporting system. PI-RADS was created to diminish variation, unify image interpretation and help reproducibility between clinics. PI-RADS is an accurate way to report PCa lesions and visually mark them in a sector map (Figure 7). PI-RADS version 1 was launched in 2012 [83]. It is a 5-stage classification system to classify lesions suspicious for cancer in MRI. The stages are as follows

- PI-RADS score 1: Clinically significant cancer is highly unlikely
- PI-RADS score 2: Clinically significant cancer is unlikely to be present
- PI-RADS score 3: The presence of clinically significant cancer is equivocal
- PI-RADS score 4: Clinically significant cancer is likely to be present
- PI-RADS score 5: Clinically significant cancer is highly likely to be present
- PI-RADS score X: Component of examination inadequate or not performed

Experiences with PI-RADS version 1 revealed some limitations including the lack of uniform structure in reporting findings and no clear threshold for csPCa [99]. Only four years later PI-RADS version 2 was published [4]. The changes with the updated version include inter alia adjustments in mpMRI technical parameters. Such parameters are ADC map windowing and DCE-MRI interpretation recommendations, and also instructions on how reporting and prostate sectoring mappings should be performed. It is still too soon to interpret the long-term results of PI-RADS v 2 but recent validation studies show promising results, which

indicate low inter-reader variability within different levels of expertise [99,100]. A few studies have compared PI-RADS version 1 and version 2 and show inconsistent results [101-103]. Their sample sizes are unfortunately small and they use either Bx or RP as a reference standard, which introduces more variability. A recent systematic review and meta-analysis that evaluated PI-RADS version 2 for PCa detection assessed over 3800 patients' mpMRI results and reported a sensitivity of 0.89 (95% CI 0.86-0.92), and a specificity of 0.73 (95% CI 0.60-0.83) [104]. They also compared PI-RADS version 1 with version 2 and reported higher pooled sensitivity for version 2 (0.88 vs 0.95, p=0.04) but no difference in specificity (0.75 vs 0.73, p=0.90, respectively). Their reference standard was either whole-mount RP specimen or Bx. Other studies show similar results [105]. PI-RADS scoring system for PCa seems to be a constantly evolving process as PI-RADS version 2.1 has already been published [82]. It supports clinicians further on the technical specifications such as clarification of the DWI b-values of diffusion, and T2WI planes. The updated version also revises the sector map, and facilitates in interpretation criteria such as volume measuring.

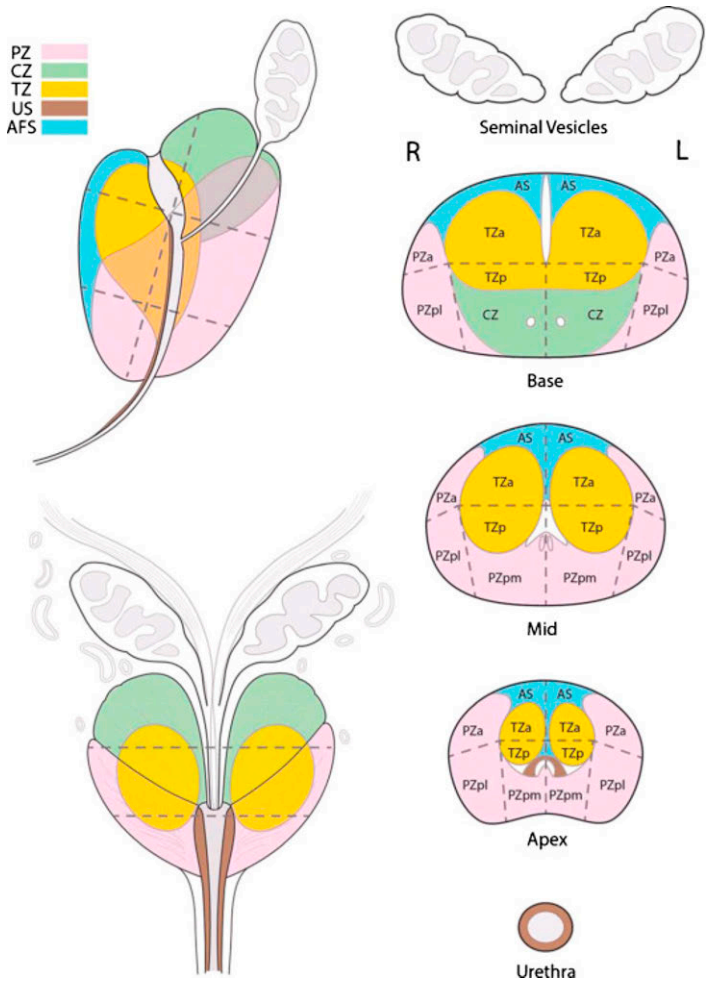

Figure 7. PI-RADS sector map for prostate cancer localization in multiparametric MRI. PZ=peripheral zone, CZ=central zone, TZ=transition zone, US=urethral sphincter, AS/AFS=anterior fibromuscular stroma, a=anterior, p=posterior, pl=posterolateral, pm=posteromedial. Reprinted from Weinreb et al. PI-RADS Prostate Imaging – Reporting and Data System: 2015, version 2, Eur Urol. Copyright 2015, with permission from Elsevier. Accessed Mar. 10, 2020.

2.3.5.4 Likert

The 5-stage Likert scoring system differs from PI-RADS because it also includes clinical data, and is designed to be used in detection, AS, recurrence and post focal treatment monitoring. The Likert scoring system rates a score between one and five and is based on the overall impression of mpMRI findings [106,107]. The analysis can be performed as lesion-based or patient-based. In contrast, PI-RADS was designed to be used only in the detection of cancer lesions. PI-RADS also focuses solely on imaging and not clinical data. Likert has been shown to be the equivalent or even perform superior to PI-RADS in detecting

any PCa [108]. Recommendations on how to report mpMRI during AS has been presented by the Prostate Cancer Radiological Estimation of Change in Sequential Evaluation (PRECISE) panel, which consists of urologists, radiologists and radiation oncologists [107]. Their consensus statement recommends that for follow-up mpMRI reports include a likelihood score between one and five for significant change in tumor characteristics, change in extension to seminal vesicles, LN or bone lesion, and the appearance of new lesions. The expert panel recommendations are necessary for congruent mpMRI reporting during AS.

2.4 Treatment of prostate cancer

2.4.1 Active surveillance and watchful waiting

Many PCas are small, localized and clinically insignificant and may not affect patients' life expectancies. These PCas are suitable for AS, which is a strategy for deferred PCa treatment. Patients who do not require immediate treatment are monitored regularly, and if no signs of cancer activation are seen, no radical treatment will be given. Prostate cancer Research International: Active Surveillance (PRIAS) protocol is the most used AS protocol in Finland [109]. Patients with a life expectancy of at least ten years are eligible for AS when they harbor a localized (≤pT2) PCa, have PSA values between 4 and 10 ng/ml, PSA density ≤0.2ng/ml², GG score of 1, and a maximum of two cancer cores in Bxs [69,110].

At one year after the diagnostic Bx a confirmatory Bx is taken. A recent meta-analysis stated that mpMRI should be performed before the confirmatory Bx, and combining TRUS Bx and FBx gives the most accurate results in finding csPCa [111]. The opposite results were seen in another randomized multicenter trial as the group was unable to prove significant differences in GG upgrading in confirmatory Bx between TRUS Bx and the FBx group [97]. However, the FBx group received only a median of two samples per target, which may have reduced the detection rates of csPCa. Thus, incorporating mpMRI with a confirmatory Bx protocol gives different results depending on the experience and volume of the center.

Monitoring AS patients includes PSA, DRE, TRUS and Bx, which all vary over three to 24 month intervals. Studies show that OS and cancer-specific survival (CSS) of AS patients at ten years after diagnosis are very good and reach values up to 93% and 99%, respectively [110,112]. Repeating Bxs during monitoring exposes patients not only to discomfort and minor side effects, such as rectal bleeding, but also to major complications such as sepsis and even death [113]. During the past decade mpMRI has become an attractive alternative to reduce the number of repeated follow-up Bxs mainly due to the high NPV of mpMRI. The hypothesis is that patients with a negative mpMRI in addition to stagnant PSA value and a normal DRE could be spared from repeat Bx. The studies show mixed results, and the limitation is that mpMRI has been shown to miss up to 30% of csPCa [91]. To date, large validation prospective studies, such as the ongoing Scandinavian Prostate Cancer Group (SPCG)-17 [114], are needed to be able to decide upon whether mpMRI can replace repeated Bxs during the follow-up in an AS protocol.

To conclude, EAU guidelines recommend mpMRI to be carried out on Bx-naïve patients with suspicion for PCa and, if possible, combining FBx with SBx in confirmatory Bx [41]. However, the volume and experience of the clinic may affect the results of mpMRI [41].

The decision of when to change from AS to active treatment is made in cooperation with the patient. Usually the criteria include Gleason score upgrading (GU) in repeated Bxs, or stage progression, but the patient's willingness to proceed to active treatment is also taken into consideration. PSA kinetics is only weakly associated with grade progression and, therefore, should not solely be the reason for change [115,116]. Differences in biomarker expression in cancer tissue in Bx have been shown to associate with increased risk of the disease progression [10,117]. However, the published results are heterogeneous and clear recommendations about the use of biomarkers in AS cannot yet be given [41].

No randomized controlled trials exist that compare contemporary AS with standard treatments. Interestingly, a recent large trial randomized over 1600 men to receive surgery, radiotherapy or active monitoring for local PCa, and the results showed no significant difference in cancer-specific mortality irrespective of the treatment assigned. However, the monitoring group encountered more metastasis and disease progression than groups with active treatments. The monitoring group, though, was monitored almost exclusively by measuring PSA. Moreover, a preplanned AS protocol with triggers for treatment was not followed thus it does not represent a contemporary AS cohort, such as PRIAS [118].

Given the heterogeneity in AS inclusion criteria, the use of mpMRI, incoherence in repeat Bx frequency and the timing of clinical follow-up, there is an unmet need for unified rules for AS. This project has been initiated and the future will show how the criteria will be formed [119]. Cancer extent and other pathology parameters in Bxs have a role [120] and accurate detection of cancer locations are important [121,122].

Watchful waiting (WW) is a reasonable choice for treatment for men with localized, ≤cT2 tumor and a life expectancy of less than ten years. It may also be an option for elderly patients with metastatic (±castration resistant) PCa and a burden of comorbidities. WW aims to refrain from active treatment in order to avoid treatment-related side effects, such as urinary incontinence, and compromises in quality of life. WW also aims to avoid treatments that do not prolong the patient's life expectancy, i.e. treatments that would do more harm than good. A study of over 19 000 men with PCa aged 66 and older who were not given curative treatment were monitored for ten years. Tumor aggressiveness did not have a role in OS, which suggests that patients died of other causes [123]. The results of other published studies report CSS rates of 82-87% for all, and 80-95% for ≤cT2 tumors with WW at 10 years [41,124].

2.4.2 Radiotherapy

External beam radiotherapy (EBRT) is a treatment option for PCa. The gold standard for EBRT is intensity-modulated radiotherapy (IMRT) with or without image-guided radiotherapy (IGRT). A dosage of 74-80 Gy is recommended for the best results to avoid BCR and least harm for the normal tissue at five years follow-up [125]. The best OS results with IGRT are seen with intermediate or high-risk, but not with low-risk, PCa patients.

IMRT is given in a fractionated manner. Hypofractioned IMRT with doses of 2.5-4 Gy is a way to reduce the injury of adjacent normal tissue, as pauses in treatment allow for DNA repair mechanisms to function [41].

EBRT can be used as a part of multimodality treatment for PCa. EBRT is often combined with ADT, which is used along with RT for four to six months with intermediate risk and 24-36 months for high-risk PCa. In a study comparing multimodality vs unimodality treatments, the OS rate of combination therapy RT with ADT (58.1%; 95% CI 49.2-66.0) was reported superior at ten years when compared to IMRT alone (39.8%; 95% CI 31.9-47.5) [126].

Other methods of radiating the prostate are also available. High-dose rate brachytherapy (HDR-BT) uses temporary implantation of a radiating substance placed near to the patient's prostate and a radiation dose is delivered in minutes. HDR-BT can be combined with IMRT for better adjustment of dosage and is a treatment alternative for intermediate-risk PCa. However, prospective randomized controlled trials comparing HDR-BT plus IMRT and HDR-BT alone are still lacking [41].

A detected BCR after RP will induce (salvage) EBRT. It has been shown to improve biochemical-free survival time compared with a wait-and-see policy and even offer a cure after BCR [41,127]. Salvage RT should be given before PSA rises >0.5ng/ml [41,128]. Salvage BT is an option after radical EBRT, when BCR is encountered [129].

2.4.3 Radical prostatectomy

The principal treatment for patients with localized csPCa and a life expectancy of over ten years is RP. The question who benefits from RP has been studied over the years. A study was conducted in randomized patients with localized PCa to RP and WW groups in the pre-PSA era [130]. After a follow-up of 13 years the study results showed a significant difference in OS, CSS and progression-free survival and significantly fewer bone metastases in favor of the RP group. Nearly ten years later in the early PSA era, another randomized controlled trial (RCT) of 731 men and follow-up time of 12 years compared RP and WW and found no significant differences in PCa-specific mortality [131]. However, patients with PSA >10ng/ml or high-risk PCa benefited significantly from RP regarding OS when compared with WW. The same study cohort was studied at 22 years, and a small benefit in all-cause mortality and increases in years of life gained from RP compared to WW was reported [132].

In the RP procedure, prostate, seminal vesicles and possibly iliac LN are removed either in an open, laparoscopic or robot-assisted laparoscopic (RALP) prostatectomy. The differences between the three techniques have been studied and in 2017 a large Cochrane review compiled the results of 446 randomized patients of two studies together [133]. Primary outcomes in these studies were CSS, urinary function and sexual quality of life. Secondary outcomes were BCR-free survival, OS, overall surgical complications, serious postoperative surgical complications, postoperative pain, hospital stay and blood transfusions. There were no significant differences in primary outcomes between the techniques. Patients who underwent laparoscopic or RALP, however, were discharged from the hospital earlier and

received fewer blood transfusions. On a guideline level, no clear recommendation of preferred surgical method can be given [134].

The role of removing pelvic LN in RP remains a debated topic. The risk of disease spreading to the pelvic LNs is assessed using preoperative risk assessment tools and nomograms, and a >5% risk of nodal metastases is an indication for LN dissection [134,135]. So far, the published reports have high risk of being biased, but implicate that removing LNs gives no improvement in oncological outcomes, but extended pelvic LN dissection provides information in staging and prognosis of PCa [136]. Furthermore, the optimal number of LNs removed is not known. The more extensive the LN dissection is, the more operation time and possible complications, such as blood loss, and lymphedema in the lower extremities. Therefore, the role of pelvic LN dissection in RP still requires statistically robust RCTs to address the issue comprehensively.

Whether to administer neoadjuvant ADT prior to RP has been evaluated in a number of studies and a comprehensive systematic Cochrane review compiled the results together [137]. The use of ADT prior to RP shows a significant reduction in positive surgical margin rate and significant improvement in LN involvement, pathological staging and organ confined (OC) rates. However, the study also reported that PSA relapse-free survival and CSS were not shown to improve and therefore the EAU Guidelines do not recommend the use of neoadjuvant ADT in clinical practice [134].

RP is initially considered a feasible treatment option for localized PCa, and patients with high PSA levels (≥20ng/ml), high-grade PCa on Bx, and advanced cancer status have poorer survival outcomes when compared with their OC counterparts [138]. However, patients with high-risk PCas undergoing RP also have reasonably good results in retrospective studies, even though approximately 30% of GG 3-5 PCas are OC at diagnosis [139,140]. The SPCG-15 is currently recruiting patients into a randomized, multi-center, prospective trial that aims to investigate how patients with locally advanced PCa benefit from RP, EBRT and possibly ADT vs EBRT and ADT only [141]. This RCT setting will hopefully validate the use of RP in advanced disease.

2.4.4 Hormonal therapy

ADT is defined as either surgical or chemical castration resulting in testosterone levels as low as <1.7 nmol/l [142]. Chemical substances include luteinizing hormone-releasing hormone (LHRH) -agonists, LHRH-antagonists, oral oestrogens and oral anti-androgens. Lack of testosterone in the body arrests the growth and development of hormone-sensitive PCas. Side effects include reduced bone mineral density, increased risk for diabetes mellitus or cardiovascular disease, diminished muscle mass, depression, loss of libido and hot flashes [143]. ADT should be the first-line treatment in metastatic PCa and it should be administered at diagnosis [134]. There is at the moment no highest level evidence on which ADT method to choose, but some data seem to support the risk of increased side effects in chemical castration over surgical castration [144].

Bilateral orchiectomy or subcapsular orchiectomy has been performed for decades and is a simple, effective and well-tolerated procedure after which castration levels of testosterone

are achieved within 12 hours. However, it is irreversible and, therefore, not suitable for intermittent treatment [145].

Similar castration levels of testosterone are achieved with long-acting LHRH-agonists, which are injected at one-, three-, six- or 12-month intervals. LHRH-agonists induce a rise in luteinizing hormone (LH) and follicle-stimulating hormone (FSH) and result in a testosterone surge. This causes the "flare" phenomenon that begins two to three days after the first injection and lasts about one week. When administered to a patient with metastases, flare may result in bone pain, acute bladder obstruction, spinal cord compression or hypercoagulation [146]. Flare can be countered with additional anti-androgen therapy (complete androgen blockade, CAB) that will suppress these symptoms. Chronic secretion of LHRH-agonist will cause LH and FSH levels to plummet and therefore testosterone levels will lower to castration levels within two to four weeks. There are no differences between the LHRH-agonists (leuprolide, buserelin, goserelin) or orchiectomy in terms of effect [147].

LHRH-antagonists lead to a rapid fall in FSH and LH levels, which cause testosterone to lower to castration levels within three days after administration. This mechanism causes no flare. There are only 1-monthly injections of one substance, degarelix, available. Degarelix has been shown to perform equally effective as the LHRH-agonists [148], and even cause less cardiovascular side effects at one year after the onset of treatment [149]. The long-term side effect profile of degarelix vs LHRH-agonist (leuprolin) are under investigation and the results are expected in the near future [150].

Anti-androgens are either steroidal (cyproterone acetate) or non-steroidal (bicalutamide) and they block androgen receptors (AR) and thereby they result in a compensatory rise in testosterone levels. Their side effect profile is usually better tolerated and they provide better bone-density than LHRH-antagonists because they do not cause testosterone to drop to castration levels [151]. Bicalutamide is widely used as an anti-androgen in Finland and it can be used as monotherapy or as part of CAB. Non-steroidal anti-androgen monotherapy for advanced PCa has been shown to be inferior in performance when compared with LHRH-agonists or surgical castration in terms of OS, clinical progression and treatment failure, therefore monotherapy with bicalutamide is not recommended [152].

Administering oestrogen results in testosterone suppression and is equally effective in treating PCa as LHRH-agonists. However, oestrogens have a different risk profile and their use is associated with increased risk for cardiovascular mortality and thromboembolic complications. Their use is not recommended as a first-line treatment [153].

Intermittent androgen deprivation therapy (IADT) is a treatment option for some well-informed patients harboring M1a-b PCa. Allegedly quality of life is better when administering IADT but trials have so far not been able to find whether IADT is inferior to continuous ADT. Treatment cycles are given at 3-6-month intervals and IADT can be given when there is no clinical progression of PCa, when the patient understands the risks of possible incomplete castration, and during monitoring PSA responds to treatment [134].

In addition to ADT, new compounds have been developed to target the AR axis. Abiraterone acetate is a second-generation anti-androgen that inhibits CYP17-enzyme, which mediates steroid synthesis. Thereby, abiraterone acetate eventually blocks the synthesis of testosterone. Abiraterone acetate with prednisone (5 mg) and with ADT has been shown to

prolong OS in metastatic castration-sensitive and castration-resistant PCa in comparison to ADT only [154,155]. Another compound, enzalutamide, is a second-generation anti-androgen that has a high affinity for AR and that also blocks the translocation of AR to the cell nucleus. Enzalutamide has been shown to prolong OS among patients with nonmetastatic and metastatic castration-resistant PCa when compared to placebo [156,157]. Other novel compounds, apalutamide [158-160] and darolutamide [161-164], function identically with enzalutamide, but darolutamide does not cross the blood-brain barrier and thereby eventually causes less fatigue than other second-generation anti-androgens.

2.4.5 Other treatments

High-intensity focused ultrasound (HIFU) frequencies are emitted from a probe that is inserted near the prostate and this mechanically and thermally coagulates malignant prostatic tissue. It can be used to destroy prostatic tissue thoroughly or partially [165]. Cryotherapy can also be used to ablate the prostate. It uses needles to transmit low temperatures to prostatic tissue to freeze cells and cause protein denaturation [166]. So far, no comparative long-term studies on oncological outcomes of ablative treatments exist and they are currently not recommended for use by the EAU Guidelines [134,167].

2.5 Disease prediction

2.5.1 Follow-up after radical prostatectomy

After radical treatment, patients should be monitored for possible disease recurrence irrespective of RP, EBRT or HDR-BT. At three months after radical treatment, the aims are to ascertain that PSA levels have fallen below the limits of detection, and also to discuss with the patient any complications related to treatment. Radically treated PCa patients have been shown to suffer from treatment-related side effects such as urinary incontinence and erectile dysfunction, and also mental issues such as depression, lower general health perceptions and perceived limitations due to physical problems [168].

Six weeks after RP, the PSA value is expected to have fallen below the detection limit [169]. Different PSA assays use limits for detection between 0.1 to 0.4ng/ml [170]. If the PSA level remains elevated, it may be due to micrometastases, residual disease in the prostatic fossa or in the distant body. After EBRT, the decline in PSA to undetectable levels is slower with the interval being up to three years or even more [134]. ERBT monitoring with PSA-DT calculations may be beneficial. For example, a study showed an association of PSA-DT of 13 months with local recurrence in comparison of PSA-DT of three months with distant metastases [171]. PSA testing at only three- to six-month intervals is sufficient for follow-up for the first two years, and thereafter biannually [172]. BCR can be seen with approximately 30% of radically treated patients and most likely during the first seven years after RP [173,174]. However, BCR does not mean the clinical manifestation of recurrent PCa, as this can only be seen in about 15% of patients with BCR. Short PSA-DT and short interval to BCR after radical treatment are risk factors for poor outcome [175].

2.5.2 Nomograms

There are a number of different pre-treatment risk stratification nomograms that are used for predicting the extent of PCa and pathological stage at RP. The original idea of nomograms was to predict PCa death of untreated men, who had recently been diagnosed with PCa [176]. However, many nomograms have been developed that also use PCa cohorts of treated men and BCR as an end-point and thus have a preselected patient cohort, which may skew the results [177]. Some tools use a combination of clinical variables and imaging data to predict different stages of PCa, but validation of these nomograms is still needed before they can be accepted for wider clinical use [178-180]. mpMRI is expected to outperform clinical nomograms in PCa risk prediction [181] as is also discussed in Study IV in this PhD thesis.

The hitherto validated, established risk stratification tools use clinical variables in the calculation. A large Swedish population-based registry study in which more than 154 000 treated and untreated men with PCa were assessed for PCa death to compare different risk nomograms [182]. Among the best performing tools were the Memorial Sloan Kettering Cancer Center (MSKCC) nomogram and Cancer of the Prostate Risk Assessment (CAPRA) Score. However, Partin tables were not included in the study.

2.5.2.1 Cancer of the Prostate Risk Assessment (CAPRA)

The CAPRA score is a preoperative assessment score for BCR after RP. The original study that presented CAPRA, was published in 2005, and included a cohort of over 1400 men who were diagnosed with PCa between 1992 and 2001, and who had undergone a RP with no neoadjuvant or adjuvant radiation or hormonal therapy [183]. The variables that CAPRA evaluate are preoperative PSA, GS, cT stage, Bx results and age. Disease recurrence is defined as PSA ≥0.2ng/ml in two consecutive samples in more than six months after RP (Figure 8).

Variable	Level	Points	Variable	Level	Points
PSA	2.0–6	0	T stage	T1/T2	0
	6.1–10	1		T3a	1
	10.1–20	2			
	20.1–30	3	% pos bx	<34%	0
	>30	4		≥34%	1
Gleason	1-3/1–3	0			
	1-3/4–5	1	Age	<50	0
	4-5/1–5	3		≥50	1

Figure 8. The CAPRA scoring system. Scores 0-2 indicate low risk, 3-5 intermediate risk and 6-10 high risk for disease recurrence after radical prostatectomy. Reprinted from Brajtbord et al. The CAPRA Score at 10 Years: Contemporary Perspectives and Analysis of Supporting Studies. Eur Urol. Copyright 2017, with permission from Elsevier, accessed Mar. 10, 2020.

CAPRA-S is a predictive nomogram for PCa recurrence after RP. In addition to preoperative CAPRA variables, it also accounts for extraprostatic extension (EPE), seminal vesicle invasion (SVI), lymph node metastases (LNM), pTNM scores and surgical margin status (Figure 9) [184].

Variable	Level	Points	Variable	Level	Points
PSA	0–6	0	Gleason	2-6	0
	6.01–10	1		3 + 4	1
	10.01–20	2		4 + 3	2
	>20	3		8–10	3
SM	Negative	0	ECE	No	0
	Positive	2		Yes	1
SVI	No	0	LNI	No	0
	Yes	2		Yes	1

Figure 9. The CAPRA-S scoring system. Scores 0-2 indicate low risk, 3-5 intermediate risk and 6-10 high risk for disease recurrence after radical prostatectomy. Reprinted from Brajtbord et al. The CAPRA Score at 10 Years: Contemporary Perspectives and Analysis of Supporting Studies. Eur Urol. Copyright 2017, with permission from Elsevier, accessed Mar. 24, 2020.

Where CAPRA and CAPRA-S have been developed for localized PCa, Japan CAPRA (J-CAPRA) is a risk nomogram for locally advanced or metastatic PCa treated with ADT (Figure 10). All three CAPRA scores (CAPRA, CAPRA-S, J-CAPRA) have been evaluated recently and reported to perform effectively in a number of validation studies over the span of a decade [185].

Variable	Level	Points	Variable	Level	Points
PSA	0–20	0	T stage	T1a–2a	0
	20–100	1		T2b–3a	1
	100–500	2		T3b	2
	>500	3		T4	3
Gleason	2–6	0	N stage	N1	1
	7	1	M stage	M1	3
	8–10	2			

Figure 10. The J-CAPRA scoring system. Scores 0-2 indicate low risk, 3-5 intermediate risk and 6-10 high risk for disease progression among patients with locally advanced prostate cancer using androgen deprivation therapy. Reprinted from Brajtbord et al. The CAPRA Score at 10 Years: Contemporary Perspectives

and Analysis of Supporting Studies. Eur Urol. Copyright 2017, with permission from Elsevier, accessed Mar. 24, 2020.

2.5.2.2 The Memorial Sloan Kettering Cancer Center (MSKCC) nomogram

It is likely that the most clinically relevant MSKCC nomogram predicts the probability of PCa progressing to LN prior to RP [186]. MSKCC provides different nomograms for pre-RP, post-RP and salvage radiation therapy patients and the risk calculation nomograms are available on their website (https://www.mskcc.org/nomograms/prostate). The variables MSKCC uses are preoperative PSA, age, GS, and cT stage. If available, positive Bx cores are also calculated.

2.5.2.3 Partin tables

Partin tables use preoperative data to predict pathological stage in men with localized (≤cT2b) PCa. Partin et al. published their study in 1993 [187]. The authors studied a cohort of 703 men with clinically localized PCa, and used GS and PSA combined with clinical stage for predicting their pathological stage. The study was conducted at a time when PSA had recently been accepted into clinical use and, as treatment protocols and Gleason scoring system have evolved, a few updates on the tables have therefore been published [188,189]. The Partin tables (Table 4) calculate the probability of different stages of PCa. They seem to perform equally good as the MSKCC nomogram in predicting the presence of LN invasion in a recent meta-analysis. However, Partin tables are developed for localized PCa whereas MSKCC has different risk calculators for localized and locally advanced or metastasized PCa [135].

PSA ng/ml	Pathological stage	Biopsy Gleason score				
		6	3+4	4+3	8	9-10
Clinical stage T1c (*n* = 4380)						
0–2.5	OC (*n* = 289)	93 (91–95)	83 (78–87)	80 (74–85)	79 (72–85)	74 (61–83)
	EPE (*n* = 21)	7 (5–8)	15 (11–20)	17 (12–22)	18 (12–24)	20 (12–29)
	SV+ (*n* = 4)	0 (0–1)	2 (0–3)	3 (1–6)	3 (1–6)	5 (1–12)
	LN+ (*n* = 0)	0 (0–0)	0 (0–1)	0 (0–2)	0 (0–2)	2 (0–6)
2.6–4.0	OC (*n* = 751)	87 (85–89)	71 (67–75)	66 (60–71)	65 (57–72)	56 (44–67)
	EPE (*n* = 133)	12 (10–14)	25 (22–29)	27 (22–32)	28 (22–34)	29 (20–40)
	SV+ (*n* = 10)	0 (0–1)	2 (1–4)	4 (2–7)	4 (2–8)	7 (3–12)
	LN+ (*n* = 4)	0 (0–0)	1 (0–2)	3 (1–5)	3 (1–6)	8 (3–16)
4.1–6.0	OC (*n* = 1439)	84 (83–86)	66 (63–69)	60 (55–65)	59 (51–66)	50 (38–60)
	EPE (*n* = 371)	15 (13–16)	29 (26–33)	31 (26–36)	32 (25–38)	32 (23–42)
	SV+ (*n* = 37)	1 (0–1)	4 (2–5)	6 (4–9)	6 (4–10)	10 (5–16)
	LN+ (*n* = 11)	0 (0–0)	1 (0–2)	3 (2–5)	3 (1–6)	8 (4–15)
6.1–10.0	OC (*n* = 686)	80 (78–82)	59 (55–63)	53 (47–58)	52 (44–59)	42 (31–52)
	EPE (*n* = 226)	18 (16–20)	34 (30–38)	35 (30–40)	36 (29–43)	36 (26–46)
	SV+ (*n* = 36)	1 (1–2)	6 (4–8)	9 (6–13)	9 (5–14)	14 (8–21)
	LN+ (*n* = 8)	0 (0–0)	1 (0–2)	3 (1–5)	3 (1–6)	8 (4–14)
>10.0	OC (*n* = 191)	69 (64–74)	42 (36–48)	34 (28–40)	33 (26–40)	23 (15–32)
	EPE (*n* = 121)	27 (22–31)	42 (36–47)	28 (32–45)	39 (31–47)	33 (24–44)
	SV+ (*n* = 28)	3 (2–5)	13 (9–18)	20 (14–27)	20 (12–28)	25 (15–36)
	LN+ (*n* = 14)	0 (0–1)	3 (1–5)	8 (4–14)	8 (3–14)	18 (9–30)
Clinical stage T2a (*n* = 897)						
0–2.5	OC (*n* = 140)	90 (87–92)	76 (70–81)	72 (65–79)	71 (62–79)	65 (51–76)
	EPE (*n* = 23)	10 (7–13)	22 (17–28)	24 (17–30)	24 (18–33)	27 (18–39)
	SV+ (*n* = 1)	0 (0–1)	2 (0–4)	3 (1–7)	3 (1–7)	6 (1–13)
	LN+ (*n* = 1)	0 (0–0)	0 (0–1)	1 (0–4)	1 (0–3)	2 (0–9)
2.6–4.0	OC (*n* = 139)	82 (78–84)	61 (56–66)	56 (48–62)	54 (46–63)	45 (33–56)
	EPE (*n* = 52)	18 (15–21)	34 (29–39)	35 (29–42)	36 (29–44)	36 (26–49)
	SV+ (*n* = 5)	1 (0–1)	3 (1–5)	5 (2–8)	5 (2–9)	7 (3–14)
	LN+ (*n* = 5)	0 (0–0)	1 (0–3)	4 (1–8)	4 (1–10)	11 (4–23)
4.1–6.0	OC (*n* = 183)	78 (74–81)	56 (51–60)	49 (43–56)	48 (40–56)	39 (28–50)
	EPE (*n* = 91)	21 (18–24)	38 (34–43)	39 (33–46)	40 (32–48)	39 (28–50)
	SV+ (*n* = 8)	1 (1–1)	4 (3–6)	7 (4–10)	7 (4–11)	10 (5–16)
	LN+ (*n* = 3)	0 (0–0)	2 (1–3)	4 (2–7)	4 (2–8)	11 (4–21)
6.1–10.0	OC (*n* = 104)	73 (68–77)	48 (43–54)	42 (36–49)	41 (33–50)	32 (23–43)
	EPE (*n* = 72)	26 (22–30)	44 (39–49)	44 (37–50)	45 (36–52)	43 (31–54)
	SV+ (*n* = 10)	1 (1–2)	6 (4–9)	10 (6–15)	10 (5–16)	14 (7–22)
	LN+ (*n* = 4)	0 (0–0)	1 (1–3)	4 (2–7)	4 (1–8)	10 (4–20)
>10.0	OC (*n* = 22)	60 (53–66)	32 (26–39)	25 (20–31)	24 (18–32)	16 (10–24)
	EPE (*n* = 22)	36 (30–42)	50 (43–56)	44 (36–53)	45 (35–55)	37 (25–49)
	SV+ (*n* = 10)	4 (2–6)	14 (8–20)	20 (12–29)	20 (11–30)	24 (13–38)
	LN+ (*n* = 2)	1 (0–2)	4 (2–7)	10 (4–18)	10 (4–20)	22 (10–37)
Clinical stage T2b or T2c (*n* = 352)						
0–2.5	OC (*n* = 26)	82 (76–87)	61 (52–70)	55 (45–66)	54 (44–66)	45 (32–60)
	EPE (*n* = 13)	17 (12–23)	33 (25–42)	34 (25–44)	35 (24–46)	35 (23–48)
	SV+ (*n* = 0)	1 (0–2)	5 (1–10)	8 (2–16)	8 (2–16)	13 (3–24)
	LN+ (*n* = 0)	0 (0–0)	1 (0–3)	2 (0–9)	3 (0–9)	7 (0–21)
2.6–4.0	OC (*n* = 27)	70 (63–75)	44 (37–51)	36 (29–44)	35 (27–44)	24 (16–35)
	EPE (*n* = 30)	28 (22–35)	46 (39–53)	43 (35–51)	44 (34–53)	37 (26–51)
	SV+ (*n* = 3)	2 (1–3)	6 (3–10)	10 (5–16)	10 (5–17)	13 (6–23)
	LN+ (*n* = 2)	1 (0–2)	4 (2–8)	11 (5–20)	11 (4–21)	25 (12–42)
4.1–6.0	OC (*n* = 52)	64 (58–70)	38 (32–44)	30 (24–37)	30 (22–37)	20 (13–29)
	EPE (*n* = 45)	32 (27–39)	49 (42–56)	45 (38–52)	46 (37–55)	38 (26–51)
	SV+ (*n* = 14)	2 (1–4)	9 (6–13)	14 (9–20)	13 (8–21)	17 (9–28)
	LN+ (*n* = 12)	1 (0–2)	4 (2–8)	11 (5–17)	11 (5–19)	24 (12–40)
6.1–10.0	OC (*n* = 25)	58 (50–65)	31 (25–37)	24 (19–31)	24 (18–31)	16 (10–23)
	EPE (*n* = 36)	38 (32–45)	52 (46–59)	47 (40–55)	48 (39–57)	40 (28–52)
	SV+ (*n* = 7)	4 (2–6)	12 (8–18)	19 (12–25)	18 (10–26)	23 (12–34)
	LN+ (*n* = 5)	1 (0–2)	4 (2–7)	10 (5–16)	10 (5–18)	22 (10–35)
>10.0	OC (*n* = 8)	42 (34–50)	17 (13–23)	12 (8–16)	11 (8–16)	6 (4–11)
	EPE (*n* = 21)	47 (39–55)	50 (41–59)	39 (30–49)	40 (28–51)	27 (18–40)
	SV+ (*n* = 18)	9 (5–14)	23 (15–33)	30 (20–41)	29 (18–42)	30 (17–45)
	LN+ (*n* = 8)	2 (0–4)	9 (4–16)	20 (10–31)	20 (9–32)	36 (20–53)

Table 4. Partin tables. Predicted probability (95% CI) of pathological stage according to clinical stage (cTNM), PSA level, and biopsy Gleason score. EPE=extraprostatic extension; LN+=lymph node involvement; OC=organ confined; RP=radical prostatectomy; SV+=seminal vesicle invasion. Modified from Eifler et al. An updated prostate cancer staging nomogram (Partin tables) based on cases from 2006 to 2011. BJU Int, Copyright 2013, 111, 22-9. Reused with permission under a Creative Commons Attributions License, accessed Mar. 25, 2020.

2.5.3 Biomarkers in prostate cancer

Biomarkers are biological molecules found in body fluids or tissues that can be measured and evaluated as a sign of abnormal or normal biological condition. They can be used for screening, diagnosis, prognosis and monitoring response to treatments.

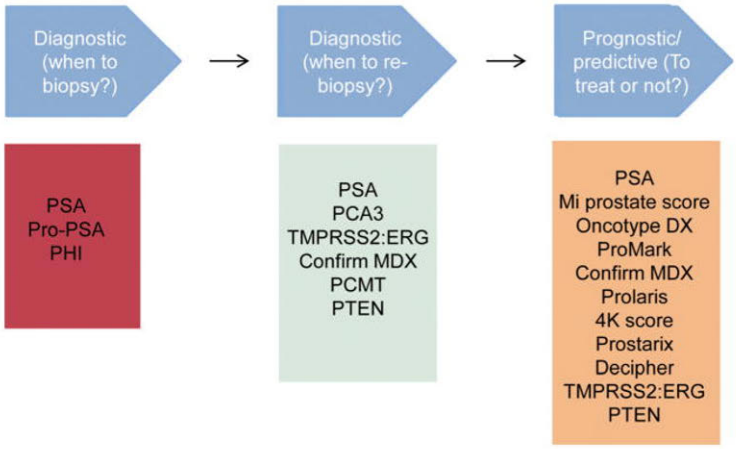

Figure 11. Clinically validated and novel prostate cancer biomarkers for prostate cancer diagnosis and disease prediction. Modified from Saini. PSA and beyond: alternative prostate cancer biomarkers. Copyright 2016. Cell Oncol (Dordr.). Reused with permission accessed Mar. 5, 2020.

2.5.3.1 PTEN

PTEN gene and its corresponding protein act as an antagonizing enzyme in the PI3K pathway, i.e. PTEN is a tumor-suppressor gene. PTEN is important in cell cycle progression, apoptosis, cellular proliferation, invasion and differentiation. It also seems to mediate some immune system activities. Inactivating mutations of tumor suppressor gene PTEN leads to PI3K activity and up-regulation of Akt/mTOR oncogenic signaling pathways, which cause activation of cellular mechanisms typical of cancer increase. PTEN loss is encountered in around 20% of primary PCa samples and in up to 50% of castration-resistant tumors, and due to this characteristic performance PTEN loss may help in distinguishing between aggressive and indolent PCas [190]. PTEN loss is therefore associated with adverse oncological outcome [191]. It has also been shown to associate with GU in AS [10], GU in RP, and BCR after RP [9,192,193]. Furthermore, PTEN loss has been shown to associate with a metastatic PCa becoming castration resistant during ADT [9]. PTEN loss can be detected in prostate tissue specimens by immunostaining [194].

2.5.3.2 ERG

Fusion of the AR regulated transmembrane protease serine 2 (TMPRSS2) with an oncogene v-ets avian erythroblastosis virus E26 oncogene homolog gene leads to AR-mediated cellular functions to accelerate and it is related to PCa progression and aggressiveness. TMPRSS2:ERG fusion and its corresponding protein expression (ERG) is found in body fluids and tissue and can be detected in 36-78% of primary PCa. The literature on the role of ERG in predicting PCa prognosis is inconsistent but ERG seems to act in concert with PTEN [9-11,191,195]. However, the prognostic significance of ERG in PCa as a single marker is unclear, and whether ERG positive or negative staining in tissue specimens associates with adverse findings is still debated [11,191,195]. However, in combination with other biomarkers, such as PTEN and prostate cancer antigen 3 (PCA3), it may be useful in PCa detection [9-11,191,196].

2.5.3.3 Others

Prostate Health Index (PHI) is a blood test that combines the inactive proenzyme form of PSA (proPSA), free circulating PSA (fPSA) and actual PSA [197]. A large meta-analysis comprising over 2900 men showed that PHI detected PCa with more accuracy than fPSA at the first Bx among men with PSA between 2 and 10 ng/ml [198].

PCA3 is a PCa specific antigen. It is not detected in benign prostate tissue, but is highly expressed in PCa. The PCA3 score is obtained in urine after manipulation of the prostate by DRE. The most studied benefit for PCA3 is its ability to predict malignancy in men with an elevated PSA and a prior negative Bx [196,197].

There are a number of other tests that are commercially available, but not yet officially approved for clinical use. These tests include the Mi-Prostate score test (incorporating blood PSA levels and urinary levels of ERG and PCA3 for prostate risk assessment); the Oncotype DX test (a validated multi-gene expression assay used as a predictor for aggressive PCa in Bx specimen); the ProMark test (a validated immunofluorescence analysis of eight proteins in Bx tissue that predict PCa aggressiveness); the Confirm MDx test (a DNA methylation level test used in identifying PCa among men with negative Bx); the Prolaris test (a gene test for PCa aggressiveness); the Prostate Core Mitomic test (a mitochondrial DNA alteration test for PCa detection); the 4K score test (measurements of total PSA, fPSA, intact PSA, human Kallikrein 2 [HK2] in blood plasma, which are later combined with clinical data for calculating the risk for csPCa); the Prostarix test (a urine metabolite test for risk stratification); and the Decipher test (a genomic test for risk progression after RP) [197]. Moreover, a model for detecting csPCa, the Stockholm-3 model (S3M), has been shown to perform better than PSA alone. The S3M consists of a combination of plasma biomarkers (PSA, fPSA, intact PSA, HK2, MSMB and MIC1), genetic markers, clinical biomarkers (age, family history, previous Bx) and a prostate examination (DRE, volume in TRUS) [199].

3. Aims of the study

The aims of the studies reported in this dissertation are as follows:

1. To evaluate the performance of repeat mpMRI among PCa patients in AS, and to study the associations between mpMRI-related parameters in predicting GU in Bxs.

2. To evaluate the differences in patient-reported discomfort, pain, and other non-infectious complications between patients undergoing SBx or FBx.

3. To evaluate the differences in biomarker PTEN and ERG status between preoperative mpMRI-visible and invisible PCa lesions, and assess the risk of BCR and non-OC PCa in an RP cohort.

4. To evaluate the added value of mpMRI against common risk stratification tools (CAPRA, Partin tables, MSKCC nomogram) in predicting BCR in an RP cohort.

4. Materials and methods

4.1 Data sources

All studies were conducted in the Department of Urology, HUS Helsinki University Hospitals, Finland. Patients' prospective data were stored and retrospective data were obtained from data banks using the patient's social security number, which is unique to each patient and is comprehensively used in Finland inter alia for identification issues relating to health and social services. The collected data include clinical variables such as age, and size of the prostate; laboratory data, such as PSA; pathology data in RP and Bx such as GG, cancer location, and extension; and imaging data, such as PI-RADS scores, ROI locations, and ROI dimensions.

4.2 Study settings

4.2.1 Study I

In the first study, the study population consisted of men who were diagnosed with PCa and monitored according to the PRIAS protocol with at least one control Bx between January 2002 and May 2015 (n=927). These data were linked to patients who had MRI of the prostate taken between January 2005 and May 2015 (n=3352). The final number of patients with <cT2, initially GS 3+3=6 PCa, ≥2 SBxs, PSA-density <0.2 ng/ml, and ≥2 MRIs of the prostate reported according to PI-RADS was 76. mpMRIs were reported according to PI-RADS v 1.0 by four uroradiologists with at least five years of experience each in interpreting prostate MRI. One or more prostate MRIs had earlier been taken in the pre-PI-RADS era for 58 patients, and these MRIs were re-reported by one uroradiologist who was blinded to the clinical data. Repeat mpMRIs were perfomed at the urologists' decision when deemed clinically necessary. Lesions identified by mpMRI were graded as either positive (PI-RADS scores 3-5) or negative (PI-RADS scores 0-2), and each lesion was separately scored and measured. When multiple lesions were seen, the one with the highest PI-RADS score was included in the analysis. When multiple equally aggressive lesions as evaluated according to the PI-RADS were seen, the largest lesion was included in the analysis.

Pathological progression was considered as GS ≥7 in any follow-up Bx during AS. Treatment change (TC) was considered as clinical stage ≥T3, ≥3 positive Bx cores, i.e. any event that discontinued AS based on the PRIAS protocol. mpMRI progression in subsequent mpMRIs was considered as an increase in PI-RADS score, appearance of new lesion(s), or an increase of ≥0.1 cm^3 in lesion size. mpMRI regression in subsequent mpMRIs was considered as a decrease in PI-RADS score, disappearance of lesions(s), or a decrease of ≥0.1 cm^3 in lesion size.

The study end-points were the association of PI-RADS and mpMRI-related parameters in predicting GS upgrading >3+3=6 and protocol-based TC from AS to active treatment. We also sought to characterize and report the changes in repeat mpMRI during AS.

4.2.2 Study II

In the second study we conducted a subanalysis of a prospective trial that was conducted between January 2015 and February 2016. The study evaluated the incidence of fluoroquinolone-resistant bacteria in prebiopsy rectal swabs and any Bx-associated complications (trial no. NCT02140502). The inclusion criteria for our study were age <80 and referral for Bx due to suspicion of PCa because of abnormal DRE findings, elevated PSA or both. A total of 262 patients were eligible for our study, 203 of whom underwent SBx and and 59 FBx. One hour before Bx 750mg Ciprofloxacin was administered as antimicrobial prophylaxis. If patients had travelled to countries with a higher risk of extended-spectrum betalactamase-producing bacteria, or had a hypersensitivity reaction to fluoroquinolones, 3g oral phosphomycin was used instead two hours before Bx. Moreover, all patients received a periprostatic 10-ml injection of 1% lidocaine under TRUS guidance prior to Bx.

The end-points of the study were pain and discomfort at 0 days reported by patients using a numeric rating scale (NRS) of zero to ten. At 30 days, pain and discomfort were measured on a scale of one (no inconvenience) to four (maximal inconvenience). Symptoms, such as hematuria, hematospermia, rectal bleeding, and fever, were also reported dichotomously (yes/no) at 30 days. Patients' willingness to undergo rebiopsy was also measured. The questionnaires used in this study were originally created for the use in the ProtecT trial [200] and later modified for the PRECISION trial [201]. We used the same questionnaires translated into Finnish.

4.2.3 Studies III-IV

In studies III and IV, we compared patients' preoperative mpMRI images to their RP specimens. A 3T MRI scanner, with the modalities of T2WI, DWI, ADC mapping, and DCE, producing 3-mm thick image slices, was in use. In total, 598 patients underwent RALP between January 2014 and September 2015. An extended lymphadenectomy was performed when the MSKCC nomogram showed >5% scores and patient had a GG ≥3 disease. Prostate glands were processed in sagittal, vertical and horizontal planes. Lymphadenectomy specimens were dissected individually. The 598 patients were linked with imaging data and 387 patients also had an mpMRI of the prostate prior to the operation. The 211 RALP patients who did not undergo a preoperative mpMRI were also monitored and any obvious selection bias was not encountered.

In study III, PI-RADS scores of 3-5 with a corresponding histopathological cancer lesion(s) were considered as mpMRI visible lesion. Histopathological cancer lesions with absent or PI-RADS score 0-2 lesion were considered as mpMRI invisible lesion(s). The study cohort was divided into subgroups in accordance to mpMRI visibility: patients with mpMRI visible lesions only (Group A, n=90), patients with both mpMRI visible and invisible lesions (Group B, n=221), and patients with mpMRI invisible lesions only (Group C, n=35) as illustrated in Figure 12.

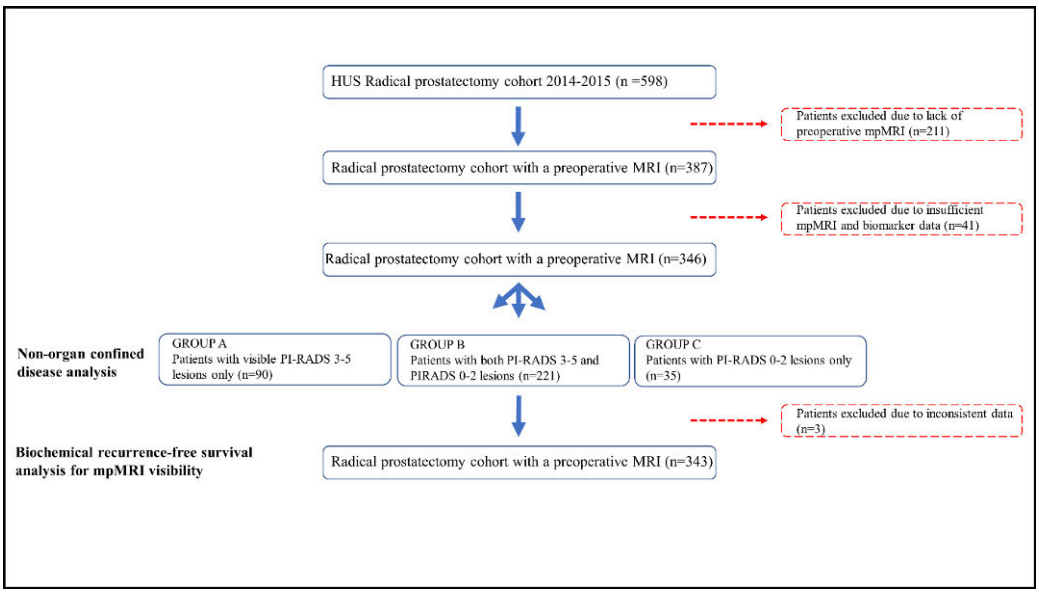

Figure 12. Flowchart of patients and division into groups A (mpMRI visible only, n = 35), B (mpMRI visible and invisible, n = 221) and C (mpMRI invisible, n = 35). Modified from Eineluoto et al., Eur Urol Focus 2020.

Tissue micro arrays (TMA) were constructed from RP tissue and organized as follows: ROIs were punched with 1.0 mm puncher core per, which represented three cores per primary ROI, and two cores per secondary and tertiary ROI. One adjacent benign core was added as a staining control. Moreover, all missed csPCa foci were marked on the slides and the most significant missed foci were punched and these represented mpMRI invisible lesions. For the TMA blocks, 4 µm thick sections were cut, stained for H&E, PTEN and ERG and mounted on electrically charged glass slides. Annotations were made by three individual uropathologists (KeS, SN and TM), see Figures 12 and 13. Antibodies for PTEN and ERG in TMAs were scored by three individual observers (JE, KoS, TM). Benign prostatic epithelium for PTEN and endothelial cells for ERG were used as positive staining controls. Cytoplasmic PTEN expression in cancer cells were dichotomously interpreted as positive or negative in comparison to benign epithelium. Cancer epithelial cell nuclear ERG staining was reported as low, intermediate or strong, although later in the final analysis these were dichotomized as negative (negative or low) or positive (intermediate or strong). The biomarker data were compared with clinical and mpMRI data. A total of 346 patients were eligible for the analysis. The study end-points were used to assess whether pathology-verified PCa lesions in RP specimen differed in PTEN and ERG status between mpMRI invisible and mpMRI visible lesions. In addition, biomarker expression was compared with preoperative PI-RADS scores, BCR and non-OC stages of cancer, including SVI, LNM and EPE.

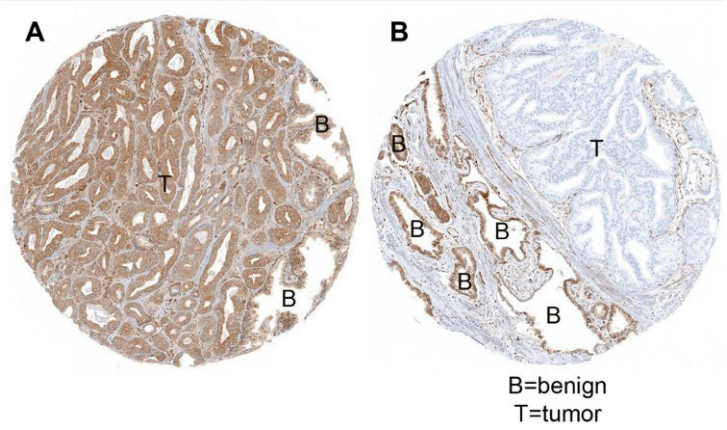

Figure 13. Immunohistochemical staining for PTEN. A) PTEN Negative (intact) in benign and tumor tissue; B) PTEN Loss in tumor but not in benign tissue. Reprinted from Lotan et al. PTEN loss as determined by clinical-grade immunohistochemistry assay is associated with worse recurrence-free survival in prostate cancer. Eur Urol Focus, Copyright 2016, with permission from Elsevier, accessed Mar. 10, 2020.

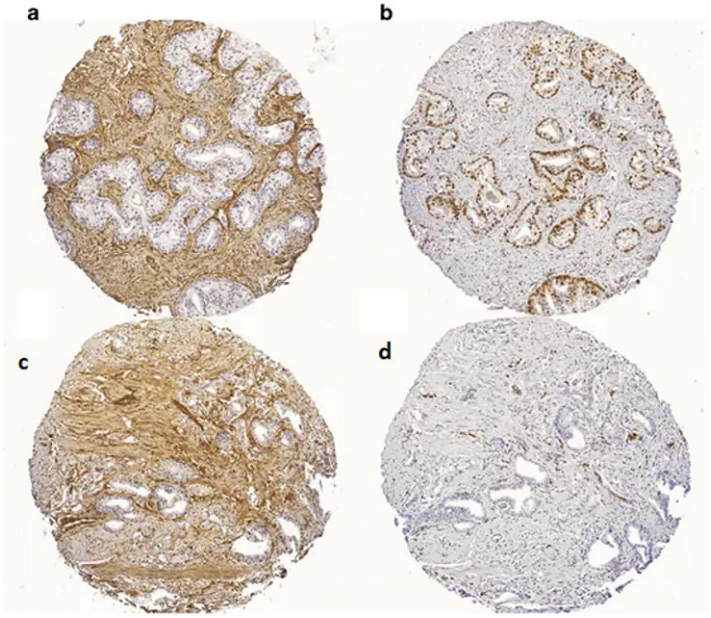

Figure 14. Immunohistochemical stainings for PTEN and ERG. a) PTEN Loss; b) ERG Positive; c) PTEN Loss; d) ERG Negative. Reprinted by permission from Copyright Clearance Center: Nature Publishing Group. Lahdensuo et al. Loss of PTEN expression in ERG-negative prostate cancer predicts secondary therapies and leads to shorter disease-specific survival time after radical prostatectomy. Mod. Pathol. Copyright 2016.

In study IV, data for CAPRA, Partin tables and MSKCC nomograms were collected for patients and these data were compared with prospectively collected RALP cohort data, which comprised age, clinical stage, PSA, primary GS, secondary GS, number of positive Bxs, and the total number of Bxs. mpMRI data were compared with these RALP data. Partin tables include only patients with TNM ≤cT2c. Therefore, Partin tables were excluded from the analyses of scores above that. GG (≥3), cTNM (≥3) and PI-RADS (≥3) scores were dichotomized for predicting adverse findings in RP. In total, 387 patients were eligible for the analysis. Study end-points were non-OC findings (SVI, LNM, EPE) of PCa and the incremental value of preoperative risk stratification tools and mpMRI in predicting this.

4.3 Statistics

4.3.1 Study I

Pearson's $\chi 2$ test of independence and Cramer's V were used to analyze the association between the variables. All analyses were carried out using SPSS ® Statistics software (version 21; IBM, Armonk, NY, USA). A two-tailed p-value of less than 0.05 was considered significant.

4.3.2 Study II

Comparisons between the Bx groups were made using Pearson's $\chi 2$ test and the Mann-Whitney U test. The factors affecting willingness to undergo rebiopsy were assessed using logistic regression analysis. The factors studied were discomfort immediately after Bx, NRS immediately after Bx, age, Bx type (SBx or FBx), and the number of previous Bx procedures. Data were analyzed using SPSS ® Statistics software (version 23). A two-tailed p-value of less than 0.05 was considered significant.

4.3.3 Studies III-IV

In study III, Pearson's χ^2 test and Fisher's exact test were used for analyzing comparisons between mpMRI visible and invisible groups. Logistic regression including the area under the receiver operating characteristics curve (ROC AUC) was used for investigating the (1) non-OC findings (EPE, SVI, LNM) in RP and (2) BCR after RP. Kaplan-Meier survival curve analysis for BCR (two consecutive PSA values >0.2 ng/ml after RALP) and Cox proportional hazard models were performed.

In study IV, multivariable logistic regression models were run to address the relationship between adverse findings (EPE, SVI, LNM), Partin Table estimates, MSKCC preoperative nomogram, and clinical variables. Cox proportional hazards models and Kaplan-Meier survival curves for predicting BCR were constructed and analyzed. Models were evaluated with and without mpMRI using decision curve analysis, ROC AUC curve and the multiparametric Wald test. Imputation of missing values by chained equations was used for 81 patients who had missing values for positive and total Bx cores [202].

For both studies, a two-tailed p-value of less than 0.05 was considered significant. R Statistical Software v. 3.6.1 was used for statistical analyses using the packages survival and mice for study III, and, in addition to those, precrec and mfp for study IV [203].

4.4 Ethics statement

The studies were approved by the Institutional Ethics Committee of Helsinki University Hospital. The Committee's approval waived the need for patient consent in the retrospective setting of studies I and III-IV. Study II was prospective and all participating patients gave their written informed consent.

5. Results

5.1 Study I

The median (range) interval between the two MRIs was 24 months (4-73 months) for all patients, 41 months (5-73 months) for those patients who continued AS and 14 months (4-72 months) for those who underwent TC from AS to active treatment.

mpMRI progression in repeat mpMRIs was seen in 53/76 (69%) of the patients: a PI-RADS score increase was seen in 7 (9%), an increase in lesion size for only 8 (10%), an increase in the number of lesions in 6 (8%), and a combination of these for 32 (42%) patients (Figure 15). mpMRI images were unchanged, i.e. radiologically stable, in 18 (24%) patients. mpMRI regression, i.e. a combination of decreases in the lesions' number, size and PI-RADS score, was seen in five (7%) patients.

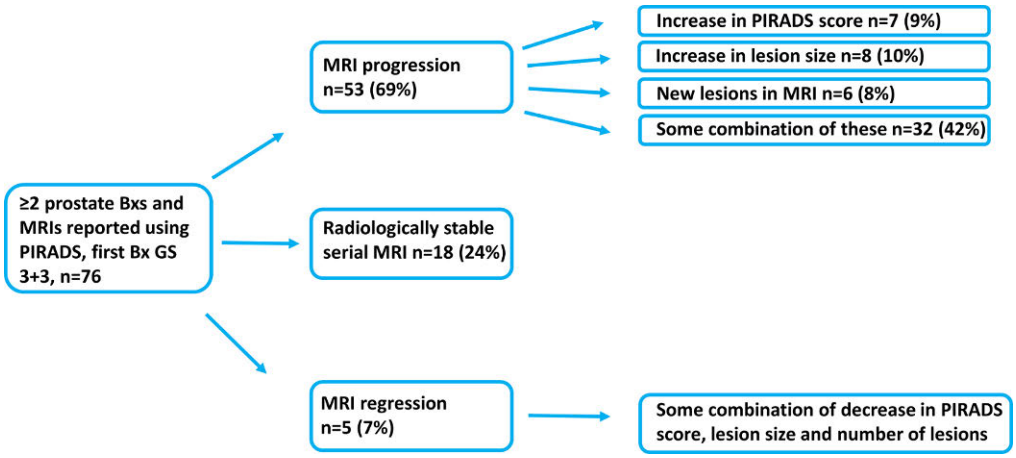

Figure 15. Serial multiparametric MRI results. Modified from Eineluoto et al. PLOS ONE, 2017.

mpMRI progression was not statistically significantly associated with GS upgrading (GU) >3+3=6 in repeated Bxs ($\chi 2 = 0.12$; $\varphi = 0.039$; $p = 1$) but it was moderately associated with TC ($\chi 2 = 4.0$; $\varphi = 0.23$; $p = 0.045$). PI-RADS scores of 4-5 in the primary mpMRI were strongly associated with GU ($\chi 2 = 8.6$; $\varphi = 0.34$; $p = 0.008$) and TC ($\chi 2 = 6.8$; $\varphi = 0.30$; $p = 0.009$), see Table 5. PI-RADS scores of 4-5 predicted GU with a specificity of 0.62 (95% CI; 0.52-0.77), and a sensitivity of 0.80 (95% CI; 0.51-0.95). Their negative and positive predictive values were 0.93 (95% CI; 0.80-0.98) and 0.34 (95% CI; 0.21-0.55). GU ≥7 in protocol-based Bxs was seen in 15/76 (20%) patients.

	mpMRI progression negative	mpMRI progression positive	Total	p-value
Treatment change negative	17	26	43	0.045
Treatment change positive	6	27	33	
Total	23	53	76	
PIRADS scores 4–5 in the first mpMRI and Gleason Score upgrading				
	No PIRADS scores 4–5	**PIRADS scores 4–5**	**Total**	**p-value**
GU negative	53	8	61	0.008
GU positive	8	7	15	
Total	61	15	76	

Abbreviations: mpMRI = Multiparametric Magnetic Resonance Imaging; GU = Gleason Score Upgrading ≥3+3; PIRADS = Prostate Imaging And Data System 1.0.

Table 5. Serial multiparametric MRI progression (an increase in tumor size, number or volume) and protocol based treatment change, cross-tabulation. Modified from Eineluoto et al. PLOS ONE, 2017.

In total 14 patients had ≥3 mpMRIs and their performance in serial mpMRI is illustrated below in Figure 16.

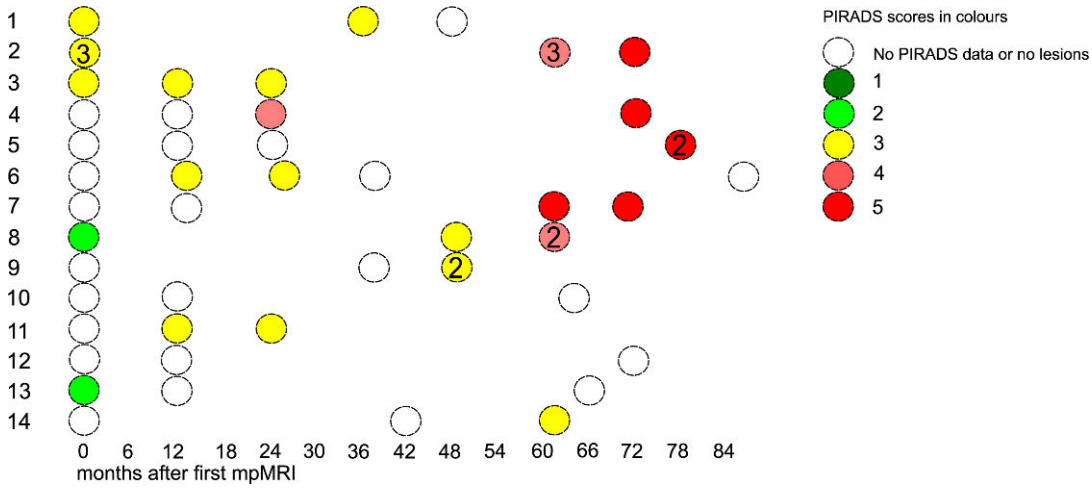

Figure 16. Characteristics of serial multiparametric MRI changes in 14 patients with ≥3 multiparametric MRIs. Each ball refers to single mpMRI and the color indicates the PI-RADS score. Number refers to number of suspicious lesions. Horizontal axis = time in moths; Vertical axis = patient number. Modified from Eineluoto et al., PLOS ONE, 2017.

5.2 Study II

Immediately after Bx, there were no differences between FBx and SBx groups in NRS pain scores (3.0 [interquartile range, IQR 1.0-5.0] vs 3.0 [IQR 2.0-5.0]; p=0.23) or median discomfort scores (4.0 [IQR 2.0-6.0] vs 5.0 [IQR 2.0-7.0]; p=0.35). At 30 days, pain scores

differed significantly between the FBx and SBx groups (12/59 [20%] vs 70/203 [34%]; p=0.043). Hematuria was also significantly less common in the FBx group (26/59 [44%] vs. 140/203 [69%]; p<0.001). At 30 days, there were no statistically significant differences between the FBx and SBx groups for rectal bleeding, hematospermia, fever, or discomfort. Response rates for the questionnaires immediately after the FBx and at 30 days after the FBx were 51/59 (86%) and 50/59 (85%). The rates for both questionnaires in the SBx group were 180/203 (89%), see Table 6.

	FBx group (n=59)		SBx group (n=203)		*p* value
	Result	R, *n* (%)	Result	R, *n* (%)	
Reported immediately after Bx		51 (86)		180 (89)	
Pain NRS score, median (IQR)	3.0 (1.0–5.0)	51 (86)	3.0 (2.0–5.0)	180 (89)	0.23 [a]
Discomfort NRS score, median (IQR)	4.0 (2.0–6.0)	51 (86)	5.0 (2.0–7.0)	180 (89)	0.35 [a]
Reported at 30 d after Bx	-	50 (85)	-	180 (89)	-
Pain, *n* (%)	12 (20)	50 (85)	70 (34)	177 (87)	**0.043** [b]
Discomfort, median score (IQR)	2.0 (1.3–2.8)	12 (20)	2.0 (1.0–2.0)	70 (34)	0.28 [a]
Hematuria, *n* (%)	26 (44)	50 (85)	140 (69)	177 (87)	**<0.001** [b]
Hematospermia, *n* (%)	23 (39)	45 (76)	94 (46)	157 (77)	0.31 [b]
Rectal bleeding, *n* (%)	11 (19)	50 (85)	65 (32)	179 (88)	0.057 [b]
Fever, *n* (%)	1 (2)	50 (85)	11 (5)	177 (87)	0.47 [b]
No/minor inconvenience for rebiopsy, *n* (%)	43 (73)	47 (80)	152 (75)	176 (87)	0.35 [b]

a Mann-Whitney U test; b Pearson's $\chi 2$ test.
IQR = interquartile range; R = responses; NRS = numeric rating scale; Bx = prostate biopsy; FBx = fusion biopsy; SBx = systematic biopsy.

Table 6. Symptoms immediately after biopsy and at 30 days after biopsy, and the number of responses to questions. Modified from Eineluoto et al. Eur Urol Oncol, 2018.

Patients who were willing to undergo a rebiopsy after initial Bx reported significantly lower median NRS pain (3.0 [IQR 2.0-5.0] vs 5.0 [IQR 4.3-6.0]; p<0.001) and discomfort scores (4.0 [IQR 2.0-6.0] vs 7.0 [5.0-8.0]; p<0.001) in comparison to the group unwilling to undergo rebiopsy (Table 7). The group willing to undergo rebiopsy reported significantly less fever (6/195 [3.1%] vs 6/28 [22%]; p=0.001) and discomfort (2.0 [IQR 1.0-2.0] vs 2.0 [IQR 2.0-3.0]; p=0.008) at 30 days after Bx in comparison to the group unwilling to undergo a rebiopsy. There were no differences in hematuria, hematospermia, hematochezia, and pain at 30 days after the procedure between the willing and unwilling groups for rebiopsy. Multivariable ordinal logistic regression analysis showed that increasing discomfort scores immediately after Bx were significantly associated with a reluctance to undergo a rebiopsy at 30 days (OR 1.5; 95% CI 1.2-1.8). There were no statistically significant association in the ordinal logistic regression analysis between the willingness to undergo rebiopsy and age of the patient (OR 0.99; 95% CI 0.95-1.03), the NRS score immediately after Bx (OR 1.1; 95% CI 0.87-1.3), the number of previous Bxs (OR 0.95; 95% CI 0.73-1.2), and Bx type (OR 0.62; 95% CI 0.29-1.3).

	Willing (n=195)		Unwilling (n=28)		*p* value
	Result	R, *n* (%)	Result	R, *n* (%)	
Reported immediately after Bx					
Pain NRS score, median (IQR)	3.0 (2.0–5.0)	194 (99)	5.0 (4.3–6.0)	28 (100)	<0.001[a]
Discomfort NRS score, median (IQR)	4.0 (2.0–6.0)	194 (99)	7.0 (5.0–8.0)	28 (100)	<0.001[a]
Reported at 30 d after Bx					
Pain, *n* (%)	67 (34)	192 (98)	14 (50)	28 (100)	0.12[b]
Discomfort, median score (IQR)	2.0 (1.0–2.0)	67 (34)	2.0 (2.0–3.0)	14 (50)	0.008[b]
Hematuria, *n* (%)	138 (71)	191 (98)	24 (86)	28 (100)	0.13[a]
Hematospermia, *n* (%)	103 (53)	175 (90)	12 (43)	22 (79)	0.70[a]
Rectal bleeding, *n* (%)	67 (34)	195 (100)	9 (32)	27 (96)	0.92[a]
Fever, *n* (%)	6 (3.1)	192 (98)	6 (22)	28 (100)	0.001[a]
Answer missing	39 patients				

a Mann-Whitney U test; b Pearson's $\chi 2$ test.
IQR = interquartile range; R = responses; NRS = numeric rating scale; Bx = prostate biopsy; SBx = systematic biopsy.

Table 7. Differences in symptoms between patients willing and unwilling to undergo repeat biopsy. Modified from Eineluoto et al. Eur Urol Oncol, 2018.

5.3 Study III

In the comparison of patients with mpMRI visible to those with mpMRI invisible lesions, the latter harbored significantly less EPE (44.6% vs. 11.4%; p<0.001), less SVI (21.1% vs 0%; p=0.003), fewer LNM (12.2% vs 0%; p=0.033), and more OC tumors (≤pT2; 55.4% vs 88.6%; p<0.001) and their lesions had lower GG. PTEN loss was encountered significantly less often in mpMRI invisible than mpMRI visible lesions (17.2% vs 43.3%; p=0.006). Positive ERG expression was more often encountered in patients with mpMRI visible lesions, but the differences between the groups were not statistically significant (Table 8).

	A: Only visible lesions, n = 90		B: Visible and invisible lesions, n = 221		C: Only invisible lesions, n = 35		*p value*		
	Result	**IQR/% of total**	**Result**	**IQR/% of total**	**Result**	**IQR/% of total**	**A vs B**	**B vs C**	**A vs C**
Median age, yr	65	60 - 69	65	60 - 69	61	55 - 65	0.8[c]	**0.001**[c]	**0.003**[c]
Median preoperative PSA, ng/ml	10.0	6.5 - 15.6	8.4	6.3 - 12.0	7.1	5.2 - 11.2	0.08[c]	0.1[c]	**0.037**[c]
Biochemical recurrence	19	21	31	14	2	5.7	0.1[a]	0.3[b]	**0.039**[a]
Gleason Grade Group at RP									
1	1	1.1	5	2.3	8	23	0.7[b]	**<0.001**[b]	**<0.001**[b]
2	30	33	90	41	18	51	0.2[a]	0.2[a]	0.06[a]
3	38	42	107	48	8	23	0.3[a]	**0.005**[a]	**0.044**[a]
4	4	4.4	6	2.7	0	0	0.5[a]	1[b]	0.6[b]
5	17	19	13	5.9	1	2.8	**0.001**[a]	0.7[b]	**0.022**[a]
Pathological stage at RP									
≤pT2	49	55	127	58	31	89	0.6[a]	**<0.001**[a]	**<0.001**[a]
Extraprostatic extension	41	46	92	42	4	11	0.5[a]	**0.001**[a]	**<0.001**[a]
Seminal vesicle infiltration	19	21	22	10	0	0	**0.008**[a]	0.052[b]	**0.003**[a]
Lymph node metastasis	11	12	10	4.5	0	0	**0.014**[a]	0.4[b]	**0.033**[b]
PTEN, visible lesions (n=311)									
Intact	50	56	129	58	–	–	0.6[a]	NA	NA
Loss	39	43	74	34	–	–	0.1[a]	NA	*A visible vs C invisible:*
NA or data missing	1	1.1	18	8.1	–	–	NA	NA	
PTEN, invisible lesions (n=256)									
Intact	–	–	139	63	25	71	NA	0.3[a]	*0.1*[a]
Loss	–	–	22	10	6	17	NA	0.2[a]	***0.006***[a]
NA or data missing	–	–	60	27	4	11	NA	NA	NA
ERG, visible lesions (n=311)									
Negative	72	80	147	67	–	–	**0.018**[a]	NA	NA
Positive	18	20	62	28	–	–	0.1[a]	NA	*A visible vs C invisible:*
NA or data missing	–	–	12	5.4	–	–	NA	NA	
ERG, invisible lesions (n=256)									
Negative	–	–	148	67	29	83	NA	0.059[a]	*0.7*[a]
Positive	–	–	25	11	3	8.6	NA	0.6[a]	*0.1*[a]
NA or data missing	–	–	48	22	3	8.6	NA	NA	NA

a Pearson's χ^2; b Fisher's exact; c Mann-Whitney U; IQR = interquartile range; RP = radical prostatectomy

Table 8. Characteristics of radical prostatectomy patients in multiparametric MRI visible and invisible groups, and characteristics of tumor lesions between groups, cross-tabulation. Modified from Eineluoto et al. Eur Urol Focus, 2020.

In ROC AUC analysis, mpMRI had a significant role in predicting non-OC findings after RP (p=0.006, Figure 17). Biomarkers did not add benefit significantly to this. In the multivariate logistic regression analysis, the clinical (age, cT≥3, preoperative PSA) and mpMRI (prostate volume, any non-OC finding) variables significantly predicted non-OC disease. PI-RADS scores ≥3, ERG or PTEN expression statuses did not predict non-OC PCa statistically significantly.

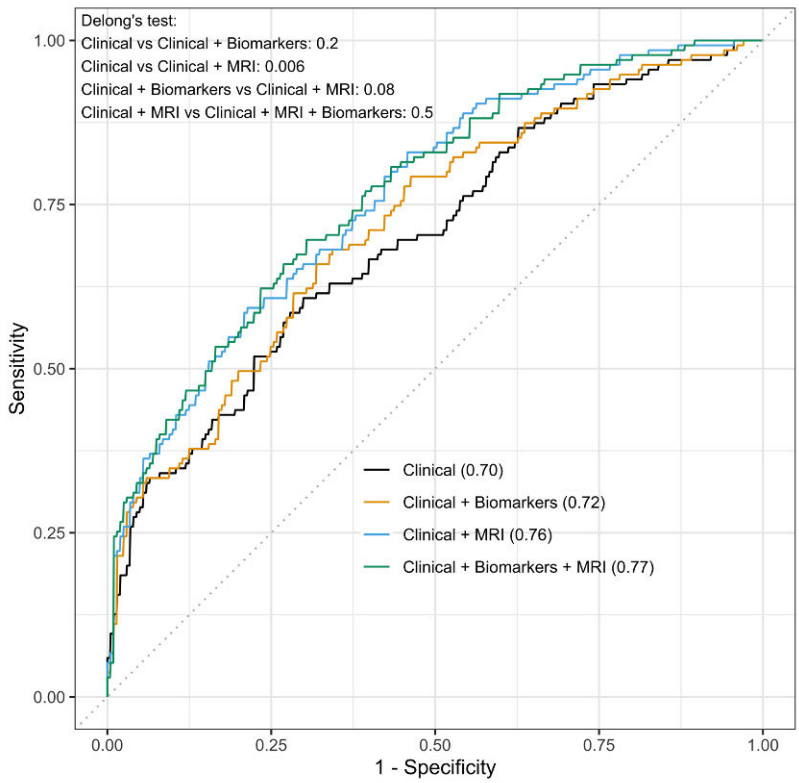

Figure 17. Prediction of non-organ confined disease at radical prostatectomy histopathological analysis. ROC AUC analysis by DeLong's test for significance between different groups of variables. Modified from Eineluoto et al. Eur Urol Focus, 2020.

BCR was encountered significantly less among patients with mpMRI invisible than those with mpMRI visible lesions (5.7% vs 21.1%; p=0.039; Table 8). Kaplan-Meier BCR-free survival curve analysis was carried out for groups A, B and C. Group C had the best BCR-free survival, but the result was not statistically significant (p=0.09; Figure 18a). The cohort was then dichotomized into groups A (mpMRI visible) vs B+C (mpMRI invisible and additional ≥1 visible lesion) and same analysis was repeated. The groups were clearly separated in the analysis but the results were not statistically significant (p=0.055; Figure 18b). For clarity, the analysis was repeated with the dichotomization of groups A +B vs C and the results were non-significantly different (p=0.1; Figure 18c).

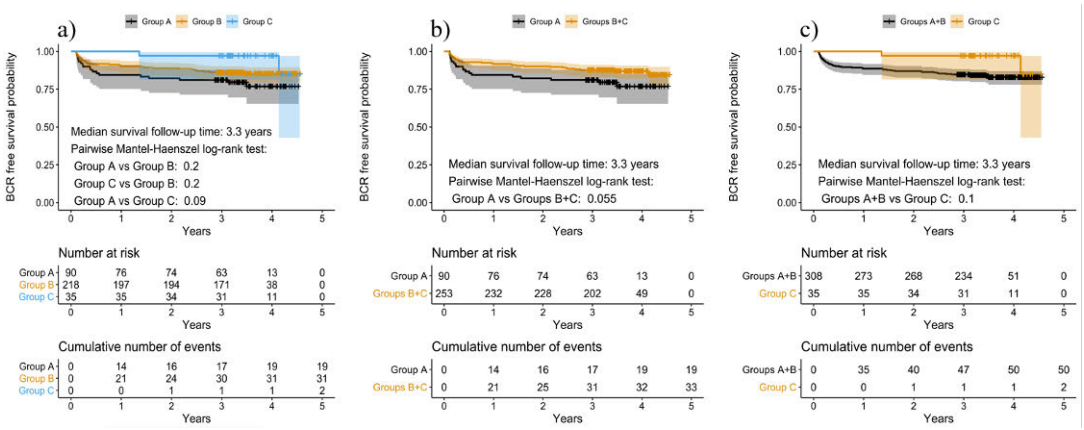

Figure 18. Biochemical recurrence-free survival curves between the groups with different multiparametric MRI visibility of prostate cancer lesions. a) Groups A vs B vs C; b) Groups A vs B + C; c) Groups A + B vs C.
Group A = multiparametric MRI visible lesions only, n = 90;
Group B = multiparametric MRI visible and invisible lesions, n = 221
Group C = multiparametric MRI invisible lesions only, n = 35.
Modified from Eineluoto et al. Eur Urol Focus 2020.

The ROC AUC analysis for BCR-free survival found significant differences (p=0.001; Figure 19) for the clinical vs clinical + MRI groups (p<0.001; Figure 19).

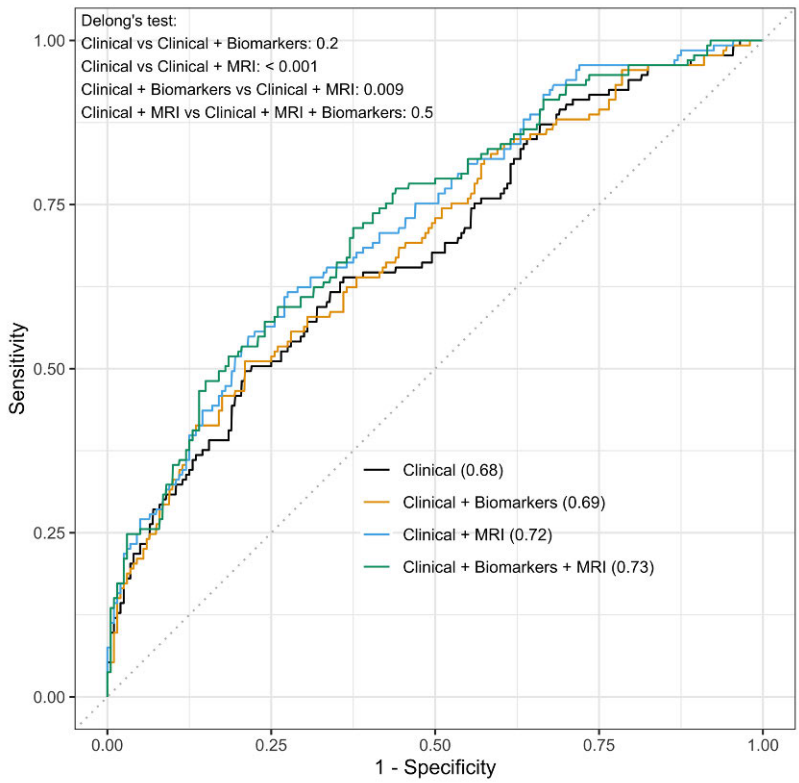

Figure 19. Prediction of biochemical recurrence after radical prostatectomy histopathological analysis. ROC AUC analysis with DeLong's test for significance between different groups of variables. Modified from Eineluoto et al. Eur Urol Focus, 2020.

PTEN loss/intact and ERG positive/negative staining did not statistically significantly differentiate the study cohort for BCR-free survival (p=0.5, and p=0.2; Figure 20). Moreover, biomarker statuses or mpMRI visibility groupings (A vs B vs C; A vs B + C) did not differ statistically significantly from a model without these variables in Cox proportional hazards models (data not shown).

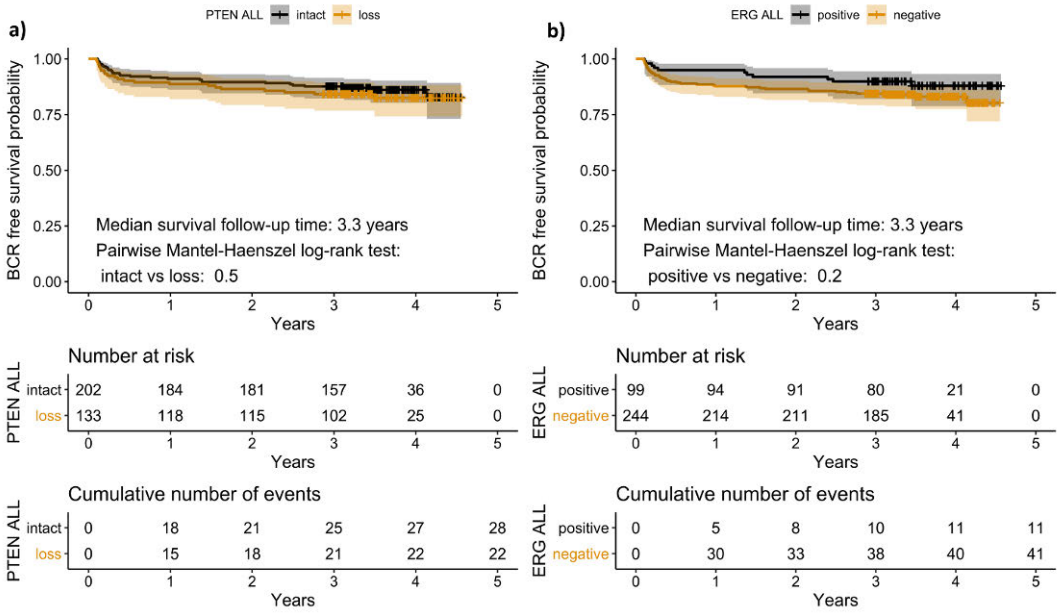

Figure 20. Biochemical recurrence-free survival between the groups with different biomarker status. a) PTEN intact/loss; b) ERG positive/negative. Modified from Eineluoto et al. Eur Urol Focus, 2020.

5.4 Study IV

In multivariable logistic regression models without mpMRI, all clinical variables except age were significantly associated with adverse findings in RP. All risk nomogram models in combination with mpMRI variables were significantly different from the models without mpMRI (Wald test, $p < 0.001$), see Table 9.

Model without mpMRI parameters				Model with mpMRI parameters			
	Estimate	OR (95% CI)	*p* value		Estimate	OR (95% CI)	*p* value
				MRI			
-	-	-	-	MRI ANY	1.420	4.14 (2.641-6.481)	**<0.001**
-	-	-	-	PI-RADS ≥ 3	1.218	3.40 (1.249-9.149)	**0.017**
-	-	-	-	MRI prostate volume	-0.013	0.99 (0.972-1.003)	0.095
PARTIN				**PARTIN + MRI**			
Partin ANY	0.026	1.03 (1.012-1.041)	**<0.001**	Partin ANY	0.025	1.03 (1.011-1.039)	**<0.001**
-	-	-	-	MRI ANY	1.277	3.59 (2.116-6.075)	**<0.001**
-	-	-	-	PI-RADS ≥ 3	0.837	2.31 (0.83-6.425)	0.110
-	-	-	-	MRI prostate volume	-0.010	0.99 (0.973-1.008)	0.235
MSKCC				**MSKCC + MRI**			
MSKCC ANY	0.053	1.05 (1.04-1.069)	**<0.001**	MSKCC ANY	0.045	1.05 (1.03-1.063)	**<0.001**
-	-	-	-	MRI ANY	1.139	3.12 (1.944-5.019)	**<0.001**
-	-	-	-	PI-RADS ≥ 3	1.090	2.97 (1.071-8.258)	**0.037**
-	-	-	-	MRI prostate volume	-0.017	0.98 (0.968-0.999)	**0.042**
CLINICAL				**CLINICAL + MRI**			
PSAPre	0.041	1.04 (1.012-1.073)	**0.008**	PSAPre	0.052	1.05 (1.017-1.091)	**0.003**
Age	0.036	1.04 (0.999-1.076)	0.059	Age	0.144	1.16 (1.033-1.291)	**0.011**
GG ≥ 3	0.508	1.67 (1.028-2.686)	**0.039**	GG ≥ 3	0.521	1.68 (1.006-2.819)	**0.048**
Positive Bx(%)	0.024	1.02 (1.012-1.036)	**<0.001**	% positive biopsies	0.022	1.02 (1.01-1.034)	**<0.001**
cT ≥ 3	1.382	3.98 (2.029-7.817)	**<0.001**	cT ≥ 3 given MRI ANY	2.047	7.74 (1.868-32.093)	**0.005**
-	-	-	-	cT ≥ 3 given MRI OC	0.426	1.53 (0.659-3.56)	0.323
-	-	-	-	MRI ANY given cT ≥ 3	1.218	3.38 (1.939-5.893)	**<0.001**
-	-	-	-	MRI ANY given cT < 3	-0.403	0.67 (0.14-3.187)	0.614
-	-	-	-	PI-RADS ≥ 3	1.104	3.02 (0.985-9.236)	0.054
-	-	-	-	MRI prostate volume	0.184	1.20 (1.002-1.442)	**0.049**
-	-	-	-	Age x MRI prostate vol.	-0.003		**0.033**
-	-	-	-	cT ≥ 3 x MRI ANY	-1.621		0.056

MRI: magnetic resonance imaging; ANY: suggestion of extraprostatic extension, seminal vesicle invasion or lymph node involvement; OC: organ-confined (≤pT2); cT: clinical stage; GG: ISUP Grade Grouping

Table 9. Regression model summaries: prediction of any adverse findings at prostatectomy. Modified from Sandeman et al. Prostate MRI added to CAPRA, MSKCC and Partin cancer nomograms significantly enhances the prediction of adverse findings and biochemical recurrence after radical prostatectomy. PLOS ONE, 2020.

In ROC AUC analyses mpMRI was added to the models and the combination of mpMRI and risk nomograms outperformed every model without mpMRI. A net benefit was seen in the decision curve analysis in models that combined mpMRI (Figure 21).

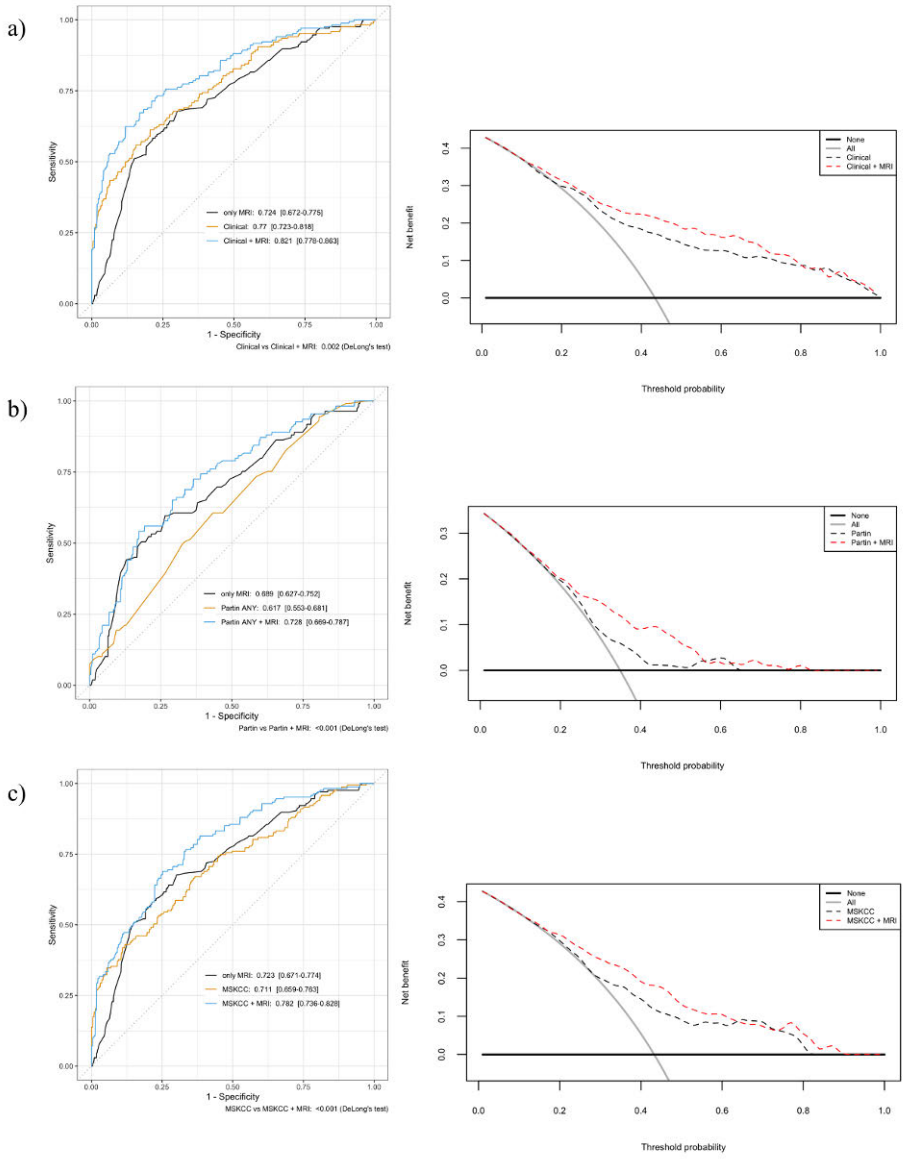

Figure 21. Additive predictive value of any adverse findings by multiparametric MRI in ROC AUC and decision curve analysis for a) clinical characteristics; b) Partin table estimates; c) MSKCC nomogram parameters. Modified from Sandeman et al. Prostate MRI added to CAPRA, MSKCC and Partin cancer nomograms significantly enhances the prediction of adverse findings and biochemical recurrence after radical prostatectomy. PLOS ONE, 2020.

In Kaplan-Meier analysis for BCR-free survival, CAPRA risk groups (high, intermediate and low) and MSKCC 3-year survival probability at 80% separated the groups statistically significantly. Furthermore, mpMRI prediction for non-OC PCa shows a significantly worse BCR-free survival time than mpMRI with OC PCa (Figure 22). All preoperative clinical variables separated the nomogram vs nomogram + mpMRI groups statistically significantly in Kaplan-Meier survival curve analysis: clinical TNM stage ≥3 vs <3, p<0.001; percentage of positive Bxs ≥50% vs <50%, p<0.001; GG≥3 vs GG<3, p<0.001; preoperative PSA <10ug/l vs ≥10ug/l, p<0.001; mpMRI prediction of OC PCa vs any sign of non-OC PCa, p=0.001; age <65 years vs ≥65 years, p=0.034.

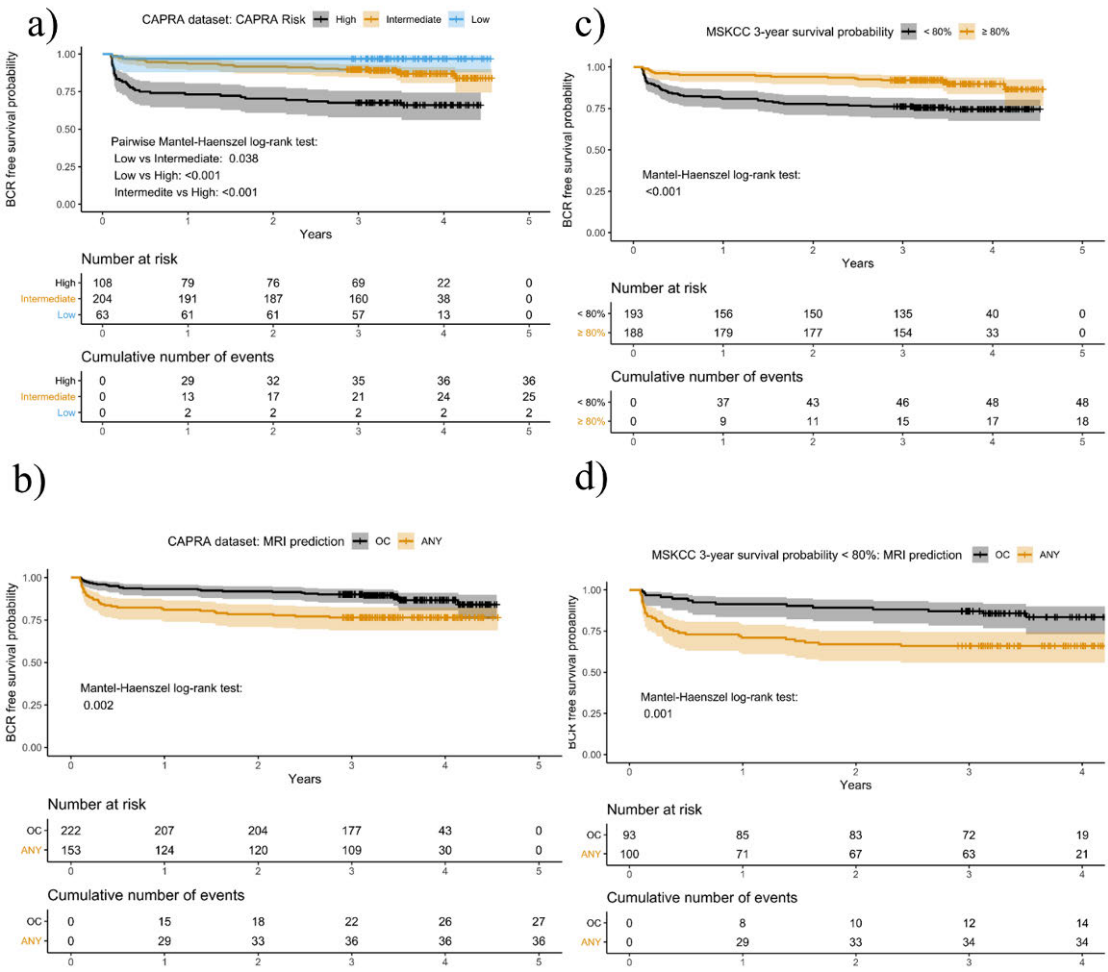

Figure 22. Biochemical recurrence-free survival. a) CAPRA nomogram results for high, intermediate and low risk groups; b) CAPRA results with multiparametric MRI indicating non-organ confined findings; c) MSKCC 3-year survival probability with a cut-off 80%; d) MSKCC with multiparametric MRI indicating non-organ confined findings. ANY=suggestion of extraprostatic extension, seminal vesicle invasion or lymph node involvement in prostate MRI;

MRI=magnetic resonance imaging; OC=organ confined. Modified from Sandeman et al. Prostate MRI added to CAPRA, MSKCC and Partin cancer nomograms significantly enhances the prediction of adverse findings and biochemical recurrence after radical prostatectomy. PLOS ONE, 2020.

6. Discussion

6.1 Study I

We found that 69% of patients had mpMRI progression in serial mpMRI during AS. Tumor progression in subsequent mpMRIs was significantly associated with TC. A negative mpMRI was also unlikely to show histological upgrading in follow-up Bxs.

Our study cohort was highly preselected. Detecting GG ≥2 PCa after two "clean" mpMRIs and multiple Bxs is unlikely, as large, high-grade tumors are usually detected earlier during surveillance. Nevertheless, 20% of the study population still showed GU and 69% showed mpMRI progression. Similar proportions of follow-up drop-outs have been seen in a large GAP 3 cohort with over 15 000 patients [204]. This suggests that the current PRIAS monitoring protocol, which relies on PSA-DT and SBxs, is insufficient for identifying csPCa. It emphasizes the importance of regular follow-ups even when patients with low-risk PCa are selected to AS. It also reveals our limited ability to find csPCa at the time of diagnosis and consequently accurately predict the behavior of PCa over time using traditional tools. Follow-up with repeated Bxs may be harmful to patients and compliance rates fall due to Bx-related complications such as infections [205,206]. mpMRI might be an additional tool for monitoring patients on AS and in delaying or even avoiding Bxs, but the literature is scarce and contradictory. At the time of writing Study I, there were no standardized criteria for mpMRI progression and regression and also our cut-off criteria were completely arbitrary. Therefore, we focused on depicting the changes of serial mpMRIs over time as illustrated in Figure 15. To date, a task force comprising urologists, radiologists and radiation oncologists published PRECISE recommendations of how to perform mpMRI during AS [107]. However, the task force still could not reach a consensus about criteria for radiological progression or regression in mpMRI.

Recently, a number of studies that evaluated serial mpMRI in AS have been published [95,98,207-211]. A study protocol close to ours was published by Hsiang et al. [207]. In their retrospective study, 129 AS patients underwent at least two consecutive mpMRIs and some radiologic reports of the study population had to be re-reviewed according to PI-RADS. Unlike in our study, every patient with PI-RADS ≥3 lesion underwent FBx in addition to SBx. Their criteria for mpMRI progression were an increase in lesion size, an increase in the number of ROIs or a doubling of index lesion volume. In our study, we did not use doubling of index lesion size as a criterion, but we used an arbitrary increase in size of ≥0.1cm^3. The Hsiang study results show similarities with ours: histopathological upgrading in Bx occurred in 24% (ours 20%), median time interval between two mpMRIs was 14 months (ours 24 months), and they could not demonstrate an association between mpMRI upgrading and GU, but PI-RADS 4-5 in the initial mpMRI associated with GU. Another multicenter study by Klotz et al. randomized 273 AS patients with GG 1 to receive either SBx or mpMRI and FBx at one year confirmatory biopsy [97]. Their end-point was the number of patients receiving GU (GG ≥2) at confirmatory Bx. The results showed no difference in GU rates between the groups. Further, they conducted a follow-up of two years for patients with GG≤1 at confirmatory Bx and mpMRI was performed at the end of follow-up [212]. Their end-point was the difference in AS failure between the groups. There were 50% fewer AS failures

and significantly fewer csPCa in the mpMRI arm at two years. In the other studies mentioned above, study settings, follow-up protocols, and triggers for additional Bx or active treatment were found to differ and the number of patients in these cohorts were small. The results of the use of mpMRI in AS have been pooled together by a few systematic reviews and meta-analyses [213,214]. Results are somewhat concordant and show that mpMRI can be used as a monitoring tool for AS and even more data supports the view that it can substitute SBx during follow-up. A negative mpMRI also seems to carry a low probability of GU.

mpMRI is recommended by the current PRIAS protocol instead of TC for patients with PSA DT <3 years, as PSA DT was found to be an insufficient variable for measuring PCa progression [64]. mpMRI shows high NPV in non-AS [89,215] and AS cohorts [216,217] and it is therefore a promising substitute for Bx in surveillance. Moreover, our results show an NPV of 0.93 and also that low PI-RADS scores were not useful in detecting high GS PCa. These findings are in concordance with other published results and they indicate the possible benefit of mpMRI in PCa diagnostics. However, longer follow-ups for studies are needed to confirm this, and also to elucidate the nature of serial mpMRI.

The limitations of this study were its retrospective nature and the lack of a standardized Bx protocol based on mpMRI findings. FBx was not available at the time of study, and therefore cognitively assessed Bxs were occasionally taken in addition to SBxs. The retrospective nature of the study limits the use of these additional cores and also the accompanying data of that time cannot be identified and evaluated. The great technological advancements in mpMRI during the study period may have affected the diagnosis and interpretation of images. For instance, early mpMRI images may not be entirely corresponding by current standards, as tumor detection with lower b-values may be poorer. However, the T2 sequences that measure tumor size remained unchanged and, therefore, we believe that these changes did not have a major impact on our study. Some of the mpMRIs in our study population had to be re-read by one radiologist. However, the radiologist was blinded to the clinical data.

The strengths of our study include the use of the structured PI-RADS scoring system for PCa lesions, the comparatively long intervals between mpMRIs and the use of a well-established monitoring protocol for AS (PRIAS). Our previous study from the pre-PI-RADS era show poor results in the association of mpMRI and GU [218]. The results of our current study are in contrast to this. The cohort spans almost a decade, and during this time considerable technological developments in MRI imaging and the implementation of PI-RADS occurred, which probably explain the differences in results between our two studies. The European Society of Urogenital Radiology Guidelines for prostate imaging were published in 2012 and these further facilitate the repeatability of the procedure. Prostate mpMRI reported in a structured format is of greater value to the clinician than a subjective narrative, which highlights the importance of structured mpMRI evaluation [91,215].

The use of mpMRI and MRI-assisted applications in AS are becoming more commonplace. Grading factors other than GG and mpMRI, such as biomarkers, are expected to emerge in the years to come. Our results support the use of mpMRI in decision making whether patients on AS should continue surveillance or opt for active treatment. mpMRI should be

incorporated into randomized AS trials to elucidate further its potential benefits, and this is being done in the current SPCG-17 trial [114].

6.2 Study II

We found FBx to be significantly associated with less pain and hematuria than SBx after 30-day period following the procedure. Pain, fever and discomfort scores differed significantly between the two groups, either willing or unwilling, to undergo rebiopsy in favor of the willing group.

Pain is a challenging concept to grasp. It is influenced by a variety of factors in the Bx procedure such as personal characteristics, transrectal probe insertion, and how local anesthetic is administered prior to the procedure [219-221]. Publications have shown that falling compliance rates during AS occur and this may be due to complications such as pain, discomfort and infections [205,222]. However, Bxs are needed in virtually all AS protocols, and as the median age for PCa diagnosis ranges between 64 and 70 years, patients probably will undergo many episodes of Bxs during years of follow-up [223]. The aim would therefore be to minimize harm in order to increase patient compliance to follow-up. Considering this mpMRI would offer benefits in two ways. First, if mpMRI can be coupled to a prognostic factor, such as a biomarker, it could help identifying patients with low-risk PCa for whom follow-up Bxs could be postponed or even avoided. Second, if mpMRI-based FBx technology reduces pain and complications, patient willingness to follow-up Bxs will be greater, as shown in our study.

The literature concerning patient experience on MRI-assisted targeted Bx is sporadic [224-227]. In contrast, SBx and pain prevention methods have been investigated more frequently [219,221,228]. With regard to pain, the optimum number of Bx cores is unknown. SBx consists of eight to 12 cores, whereas FBx uses fewer cores, usually one to four. We had a median of three cores per patient in the FBx group, and this is a mere 25% of the cores of the SBx group. This difference may partly explain the differences in pain and discomfort. Fusing MRI images to US requires more time, and this may contribute to the time the local anesthetic is allowed to function before the initiation of Bxs. Interestingly, a study showed no difference in patient-experienced pain with zero minutes vs five minutes of waiting time after administration of local anesthetic prior to Bxs [229]. We did not record the waiting times in this study, but it is unlikely that the mean exceeded five minutes as the whole FBx procedure generally lasts eight to ten minutes. Thus, the puzzle of lower pain scores of the FBx group remains unsolved.

Most, if not all, AS protocols rely on repeat Bxs during follow-up. For this reason, in our study, one of the questions was: “How inconvenient would a rebiopsy be, if needed?” In the FBx and SBx groups, 73% and 75% of the cohort answered “no or minor inconvenience”, which is in line with a previous Finnish study where over 80% of the study cohort were willing to undergo rebiopsy and 2% refused [230]. In our study only 1% (2/362) answered that rebiopsy, if needed, would cause “maximal discomfort”. The method of questioning and study setting differ between these studies but the results are in still in agreement.

Limitations of the study include the nonrandomized design, as blinding for the Bx procedure cannot be feasibly achieved under normal clinical conditions. Therefore, any bias by the urologist or patient toward the outcome of one method or the other will remain even though randomization would allow for equal distribution of confounding factors and associated biases. Moreover, the small number of patients was a limitation and the response rates to questions were occasionally moderate, which may diminish the statistical power and introduce bias into the study.

The strengths of this study, on the other hand, include its prospective setting, the use of a validated and commonly known NRS tool for measuring pain, and the 30-day questionnaire. Our results are directly reported by patients and analyzed by the authors and therefore omit any interpretation by a third party. The study cohort also included patients in a typical clinical setting and therefore our results can be generalized to everyday practice.

Given these findings, we suggest that FBx may become the preferred method of choice not only for its diagnostic accuracy but also due to its fewer associated side effects. Infections and complications after Bx such as hematuria are a major cause of hospitalization. If SBx is increasingly replaced by FBx, this may reduce Bx-related complications and, thus, cut complication-related costs and allow for the higher expenditure for the use of mpMRI. These issues were more profoundly addressed by the PRECISION trial, which is a large prospective multicenter trial that compared FBx only, to SBx [201].

6.3 Study III

We found that PTEN loss was seen significantly more often in mpMRI visible only (true positive) than mpMRI invisible only (false-negative) lesions. mpMRI visible lesions also had significantly higher GG, more EPE, SVI and LNM in RP and more frequent BCR after RP than mpMRI invisible lesions. mpMRI visibility clearly separated the Kaplan-Meier BCR-free survival curves with a median follow-up of 3.3 years, but the results did not reach the conventional criteria for statistical significance.

The characteristics of mpMRI invisible lesions is a fairly unknown chapter. mpMRI seems to miss the less aggressive (GG 1), multifocal and small (<5 mm in diameter) nonindex tumor lesions [231]. A recent study divided their patient cohort with ≥2 negative mpMRIs into Bx-naïve and prior negative Bx groups and found no difference in the detection rates for csPCa [232]. Further, a study of over 320 men with only PI-RADS ≤2 lesions reported a csPCa disease-free survival of 99.6% with a median follow-up time of 57 months [233].

Biomarkers coupled to mpMRI may facilitate the detection of csPCa and this has been addressed in a few studies. Lee et al. compared mpMRI visible vs mpMRI invisible lesions in a retrospective cohort of 48 patients and found differences in their molecular characteristics: mpMRI invisible lesions only harbored CHD1-deletions whereas SPINK1-biomarker was absent [234]. Gene expression and mpMRI visibility have been investigated and mpMRI invisible tumors were associated with favorable PCa prognosis [235]. The authors concluded that the result was not entirely explained by GG or tumor volume and that mpMRI visibility may have acted as an independent predictor. Further, the Decipher® gene panel is a commercially available test for PCa prognosis and a study that used

Decipher® reported lower panel scores and lower genetic risk for metastasis in mpMRI invisible lesions [236]. mpMRI visible tumors seem to be enriched with genes that are associated with a higher preponderance of cribriform structures and a higher mutational frequency [237]. All in all, these studies have small cohort sizes and their follow-up times were moderate.

In our study, Kaplan-Meier BCR-free survival analysis did not show a statistically significant difference between the mpMRI visible and invisible groups. We did not find mpMRI visibility to be an independent prognostic factor for PCa prognosis in comparison with other clinical variables. However, ERG rearrangement and PTEN loss occurred in 14% (28/205) and 15% (28/192) in mpMRI invisible, and 27% (80/299) and 39% (113/292) in mpMRI visible lesions, respectively. This is in line with the literature, as published studies report data for ERG rearrangement between 36-78% and PTEN losses between 18-42% of PCa cases [10,11,195]. We found no added benefit for ERG and PTEN expressions using either logistic regression analysis or Kaplan-Meier survival analysis in our study. This may be a true finding or experimental artifact arising from either the limited number of patients or the short follow-up time.

Limitations of the study comprise moderately short follow-up time, small numbers of patients in the groups only mpMRI visible (true positive) and only mpMRI invisible (false-negative), and lack of a validation cohort.

The strengths of the study include the use of RP whole-mount pathology specimen to control the accuracy of PI-RADS interpretation of the mpMRI images. Further, our cohort consisted of all RALP patients in our hospitals and there was no apparent bias for mpMRI selection.

Whether mpMRI invisible lesions affect the course of PCa will hopefully be clarified by long-term clinical studies that incorporate longitudinal imaging and follow-up data. The use of mpMRI is on the rise and knowledge on mpMRI features and characteristics accumulates rapidly. Biomarkers are a promising tool for PCa prognostication as their profiles could be defined as early as at Bxs and their features could help in the decision making prior to definitive treatment. However, their incorporation into clinical use still needs validation. The future will show whether mpMRI coupled to biomarkers may truly act as an aid for clinicians.

6.4 Study IV

We combined mpMRI with clinical parameters, Partin tables and MSKCC nomogram to predict EPE, SVI, LNM, i.e. adverse findings, in RP. We found that mpMRI significantly enhances the prediction of adverse pathology at RP when it is combined with the traditional tools for prediction. Moreover, mpMRI showed added benefit in predicting BCR when combined with CAPRA and MSKCC nomograms.

Our results are mostly in line with other published studies. A recent meta-analysis that involved more than 9700 patients pooled mpMRI results for non-OC findings together using RP as a reference standard [238]. That study reported a sensitivity of 0.57, 0.58, and 0.61, and a specificity of 0.91, 0.96, and 0.88, for EPE, SVI and overall stage T3 detection,

respectively. The use of 3T field improved the sensitivity for EPE and SVI. Heterogeneity of the studies, however, hampers the generalization of the results.

A few recent studies have addressed the added benefit of mpMRI in addition to using risk nomograms. Morlacco et al. evaluated 914 patients of which 501 patients had endorectal coil [239]. Their and our study cohorts are relatively similar regarding the risk factors (≥pT3 49% vs 44%) but differ considerably in mpMRI characteristics (1.5T mpMRI, endorectal coil and non-structured reporting vs 3T pelvic coil and structured reporting). They reported that mpMRI is beneficial for staging purposes, but their cohort was of high-risk and from the pre-PIRADS era, thus, their results may underestimate the effect of mpMRI. Further, Morlacco et al. did not report the characteristics of their non-MRI cohort, and it is therefore uncertain whether clinical decision making in the selection of patients for MRI was skewed towards those who would have benefited from imaging. Another study by Grivas et al. evaluated the added value of preoperative 3T mpMRI with endorectal coil and non-structured reporting for staging SVI using RP as a reference [240]. They compared inter alia SVI with and without mpMRI and reported substantially higher AUC values for Partin nomogram to predict SVI with (0.93) and without (0.84). Our results for the same comparison were: with 0.73 and without 0.69, and this disparity suggests a different background risk in these cohorts between the two studies. In another study, a cohort of 60 men was evaluated for mpMRI and Partin tables to predict EPE, but they did not analyze the added value of mpMRI [241]. In comparison to our results, EPE prediction by Partin tables was equally good (AUC of 0.62 vs 0.56), whereas mpMRI had significantly better performance in their study (AUC 0.82 vs 0.62). A subsequent study by the same group reported a higher detection rate of OC PCa by mpMRI than by Partin tables (AUC 0.88 vs 0.70) using RP as a reference standard [242]. Prediction of EPE for Partin tables and MSKCC were also evaluated by Feng et al., and they reported AUCs of 0.85 and 0.86, respectively [243]. When mpMRI was added to the model, AUC increased to 0.92 and 0.94, respectively. However, the studies by Gupta et al. and Feng et al. relied only on the reporting of mpMRI data of one radiologist in their study protocols and this may have contributed to some bias and diminished the effect of interreader variability in the results of their studies [241-243].

Our data suggest that mpMRI is a valuable tool in predicting BCR after RP when used along with well-known prediction tools, as was seen for the more specific high-risk CAPRA and MSKCC groups. When considering mpMRI as a standalone investigative modality, we found that mpMRI was also able to differentiate BCR survival between two groups. Our results are in line with a previous study from the pre-PI-RADS era, which reported that mpMRI helped in predicting BCR after RP in clinically localized PCa [244]. Structured imaging reporting is expected to improve its predictive value further, as adverse findings in RP are known to predict BCR. We used PI-RADS 1.0, as it was the recommended reporting system at the time of our study. By using PI-RADS 1.0 we gained a longer follow-up time and the possibility to study BCR as an end-point. The more recent PI-RADS 2.0/2.1 versions may improve diagnostic reliability and diminish inter-observer variance further [245].

When taken together, the literature and our present results support the use of preoperative mpMRI as a staging tool particularly in the prediction of EPE and SVI. However, it is not clear, whether mpMRI is an adequate staging tool for LNM. The size, location and many other features of the tumor can be assessed using mpMRI, which may affect preoperative clinical decision making and help facilitate the planning the surgical procedure, even though

there is inevitable uncertainty in predicting the presence of EPE and SVI. This was shown in a recent study in which patients, who underwent a preoperative mpMRI, were less likely to have a nerve-sparing RP and a lower likelihood for positive surgical margins [246]. A considerable proportion of node metastasis are microscopic, whereas, enlarged LNs may be reactive. To address the issues of nodal involvement, a novel nomogram that incorporates several mpMRI related variables has been developed for nodal status evaluation before RP [247]. This further encourages the use of preoperative mpMRI despite that the exact nodal evaluation seems to be suboptimal using current mpMRI techniques.

Limitations of the study include single center data and its retrospective nature. Not all RALP patients underwent mpMRI during the study period. However, in comparison to patients who did not undergo preoperative mpMRI, we found no obvious differences in their demographics. Further, pathologists are encouraged to initiate a regional reporting system similar to PI-RADS to improve translational PCa research, enhance diagnostic accuracy and better integrate mpMRI with pathology for more precise decision making.

The strengths of the study include a cohort of all RALP patients in our hospitals and no bias for mpMRI selection. We also had four radiologists who assessed and reported our mpMRIs using a structured PI-RADS system for accurate description of tumors, and also RP specimen was used as a reference for imaging.

The preoperative prostate mpMRI enhances the prediction of adverse findings at RP and BCR after RP. mpMRI should be considered as another source of information for risk stratification nomograms.

6.5 Synthesis

Taken together, these studies address the issue of how to detect as few clinically insignificant and as many clinically significant PCa as possible with the least harm for the patient. We approached this dilemma in multiple ways including clinical, imaging, laboratory and histopathological means.

Study I evaluated how mpMRI contributes to AS at diagnosis and during follow-up. From a certain perspective AS can be seen as a compromise between not treating and monitoring indolent tumors at all, and treating all initially but sparing the patient treatment related side effects. Unfortunately, a great number of patients still discontinue AS and instead opt for active treatment even though many show low-risk characteristics at subsequent RP. Undoubtedly, we need better and more refined tools to detect csPCa earlier. Prostate mpMRI may achieve this by detecting more men with csPCa at diagnosis. This will translate to fewer men initially being misclassified and probably a lowered need for initial repeat Bxs in AS protocols. Futhermore, mpMRI at diagnosis will probably result in fewer men needing AS since fewer men are diagnosed with clinically insignificant PCa. On the other hand, men with favorable mpMRI (no lesions initially and no progression during follow-up) might be candidates for reduced rebiopsy protocol. However, men should be followed-up in cases of true biological progression of PCa. The estimated rate of true biological progression is around 1-2% per year [248] thus it may be that the taking of routine Bxs can be postponed until years after diagnosis. The technical progress of mpMRI and mpMRI devices has been

rapid. During the early stage of mpMRI in early 2010s, we could not show much of a benefit of MRI in PCa AS [218]. However, less than a decade later we could report an association between mpMRI PI-RADS score 4-5 and GS upgrading in subsequent Bx in addition to transition from AS to active treatment. This suggests that serial mpMRI along with structured reporting may be useful monitoring tools in PCa AS. Nonetheless, serial mpMRI cannot as yet substitute histopathological analysis, i.e. repeated Bxs, in assessing disease characteristics due to the fact that mpMRI currently misses up to 30% of csPCa.

Repeat Bxs are the current norm in AS to detect initial misclassification and true biological progression, but they are also an inevitable burden for the patients. In study II, we evaluated this by studying patient experience after FBx and SBx. We found significant comparative differences in pain, discomfort and treatment related side effects in favor of FBx. By choosing optimal diagnostic pathways for patients we may be able to minimize treatment related side effects and enhance compliance for surveillance. We expected this to improve results in PCa treatment as fewer Bxs will be taken overall, fewer unnecessary Bxs will be taken, and plausibly more men in need of Bx will eventually comply. The aim with mpMRI is that we will be able to detect aggressive forms of PCa early on and direct them to receive adequate immediate treatments. Subsequent biomarker analysis utilizing Bxs may aid in this.

Study III focused on the characteristics of biomarkers in mpMRI visible and invisible tumors in RALP patients and reported significant differences between the groups. This is interesting as mpMRI is known for its high NPV, yet this rate varies significantly. Currently, there is ongoing debate about whether men with negative mpMRI should undergo SBx or not. Whether these false-negative mpMRI lesions possess a similar threat to a man's well-being as true positive mpMRI lesions, is currently unknown. Our results contribute to this by evaluating the surrogate markers of biological aggressiveness, and they show that mpMRI false-negative lesions seem less aggressive than mpMRI true positive lesions. PTEN and ERG in PCa prognostication are still under debate and not yet in clinical use. However, evidence concerning especially PTEN loss and its association on aggressive types of PCa seems to be consistent and PTEN may become the next biomarker adapted for clinical use. Detecting biomarkers that would help in risk stratification would be immensely important.

Study IV described the added value of mpMRI as an adjunct to traditional risk prediction nomograms in detecting adverse findings in PCa. We found that mpMRI is beneficial in detecting non-OC disease at RP and also in predicting BCR after RP. As the use of mpMRI increases continuously and guidelines recommend prostate mpMRI before first Bxs, mpMRI data would be readily available and could be added at no extra cost to the existing prediction. This would offer the possibility for PCa prediction as early as during the diagnostic phase. Nevertheless, this may be problematic due to the fact that those investigated lesions that are not detected by mpMRI cannot by definition be targeted by this modality. Hence, SBx may still play a role in the future until we discover the true nature of mpMRI invisible PCa lesions. Such data should also be validated in large, longitudinal mpMRI cohorts with long follow-up times using RP as a reference.

In the future, we will probably see a spectrum of different modalities to assess better the true nature of PCa, including prognostic biomarkers and genome sequencing. Importantly, the aim is to make PCa diagnostics and treatments more personalized. The path towards

precision medicine will be multidisciplinary in the way that PCa diagnosis and treatment decisions will be made increasingly on the basis of imaging and biomarker data in addition to clinical data. Importantly, these approaches will have to be tested prospectively in multi-center RCTs to evaluate their true clinical value to achieve this goal.

7. Conclusions

1. mpMRI is a useful tool for men with PCa to guide patient selection for AS and monitoring.

2. The FBx diagnostic pathway causes less harm for the patient when compared with the traditional SBx pathway.

3. mpMRI invisible tumors appear less aggressive than mpMRI visible tumors in terms of the following: PTEN loss, EPE, SVI, LNM, GG score and BCR after RP.

4. The addition of preoperative mpMRI data to existing prediction tools increases their predictive performance in terms of stage at RP and the prediction of time to BCR. mpMRI is currently readily available prior to RP and should be considered as an additional tool along with predictive nomograms.

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